Performance of a host response test for bacterial/viral discrimination in immunocompromised patients

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BACKGROUND

- Difficulty distinguishing bacterial infection, viral infection, and non-infectious causes of illness contributes to excess antibiotic use and antibiotic resistance
- The host response offers an alternative diagnostic strategy that overcomes limitations of pathogen-based techniques (long time to results, *a priori* suspicion, or differentiating colonization vs. infection)
- Host-based diagnostic tests rely on a functional immune system
- Host gene expression-based tests for accurately distinguishing bacterial vs. viral infection have previously been defined [1-6]
- The ability of these host gene expression signatures has not previously been adequately studied in patients with immunocompromising conditions

OBJECTIVE

- Assess the performance of a previously-developed host gene expression test [5] to distinguish bacterial infection, viral infection, and non-infectious illness in an immunocompromised cohort

METHODS

- Inclusion: (Table 1)
  - Active chemotherapy
  - HIV with CD4<200
  - Immunomodulatory agents [Disease modifying antirheumatic drugs, chronic steroids (10mg of prednisone equivalent daily for >30 days), or acute high dose steroids (60mg of prednisone equivalent for ≥3 days]
  - Solid organ transplant
- Clinical Adjudication: Cases were reviewed by two independent adjudicators. Disagreement was resolved by panel consensus. Only cases of microbiologically confirmed bacterial or viral infection were included in this study. Noninfectious subjects had negative microbiological testing and an alternative, noninfectious diagnosis. Clinical adjudication served as the reference standard.
- Host gene expression measurement: Real-time PCR was performed on TaqMan Low Density Arrays (TLDA) customized to quantify 81 previously described gene targets [7]
- Gene expression-based classification: Logistic regression model was fit on 136-subject immunocompetent cohort and then used to generate three independent probabilities (bacterial, viral, noninfection) in the immunocompromised cohort (n=134)
- Test Characteristics: Sensitivity and specificity were assessed via winner-takes-all approach (highest independent probability of the three classes determined subject's diagnosis)
- Analysis: DeLong test was used to compare AUCs between training and validation (immunocompromised) cohort. Kruskal-Wallis, Mann Whitney U test, and Chi-square tests were used to compare test probabilities and overall test accuracy

	Bacterial	Viral	NI	Total (%)
Immunocompetent Training Cohort	43	52	41	136
Immunocompromised Validation Cohort	64	28	42	134
Immunomodulatory Agent	21	16	22	59 (44.0%)
Solid Organ Transplant	25	5	8	38 (28.4%)
Chemotherapy	14	5	9	28 (20.9%)
HIV/AIDS	4	2	3	9 (6.7%)

Table 1. Number of subjects per immunocompromising condition

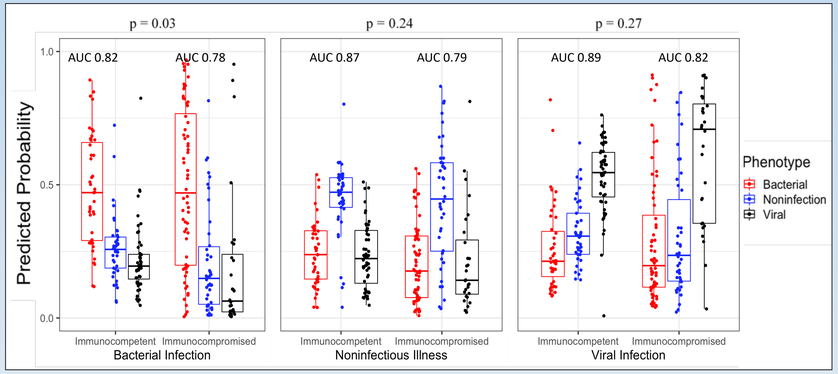

Figure 1. Illness etiology predictions. Each panel includes the predicted probabilities for the specified condition (bacterial-left, noninfectious-middle, viral-right). Colors represent the adjudicated phenotype as indicated in the figure legend.

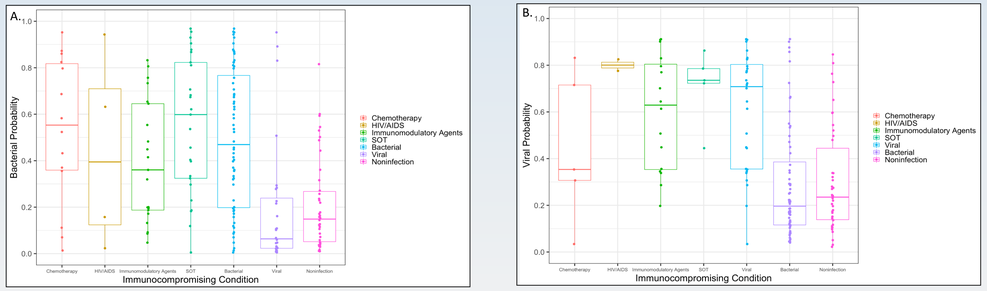

Figure 2. Bacterial (A) and Viral (B) predicted probabilities based on type of immunocompromising condition. For each specified immunocompromising condition, only subjects with bacterial infection are shown in Figure 2A where as only those with viral infection are shown in Figure 2B.

RESULTS

- **Overall accuracy of host gene expression test (Figure 1):**
  - Training cohort: 86.4% for bacterial vs non-bacterial infection, 80.8% for viral vs non-viral infection
  - Validation: 73.9% for bacterial vs non-bacterial infection (p=0.03 vs training), 75.4% for viral vs non-viral infection (p=0.24)
- No significant difference in test performance for bacterial (**Figure 2A)** or viral infection **(Figure 2B)** based on type of immunocompromising condition
- No significant difference in test performance based on number of immunocompromising conditions
  - Bacterial: 60.5% for one condition vs 73.3% for multiple (p=0.64)
  - Viral: 77.3% for one condition vs 83.3% for multiple (p=0.78)
- Since the training and validation cohorts were processed at different times, it is possible that batch differences explain the lower performance.
  - Evaluation of the entire cohort together (n=270) using LOOCV showed performance was still lower in IC subjects with respect to bacterial infection diagnosis (p=0.04) but not viral infection diagnosis or non-infectious illness (p=0.055).

CONCLUSIONS

- A host gene expression RT-qPCR test discriminated bacterial, viral, and noninfectious etiologies at a lower overall accuracy in immunocompromised patients compared to immunocompetent patients
  - Difference was only statistically significant for bacterial vs. non-bacterial disease
  - Not dependent on number or type of immunocompromising condition, though sample size of subgroups may be too small to determine statistical difference
- Despite lower performance, this host gene expression test still offers useful diagnostic information for patients with immunocompromise. Clinical utility may be further improved with alternative reporting schemes that maximize sensitivity or specificity as clinically indicated.

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