A novel host-protein assay accurately distinguishes bacterial from viral upper respiratory tract infections

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Abstract

BACKGROUND

Bacterial and viral infections are often clinically indistinguishable, particularly in upper respiratory tract infections (URTIs), which leads to antibiotic misuse. A novel assay (ImmunoXpert™) that integrates measurements of three host-response proteins (TRAIL, IP-10, and CRP) was recently developed to assist in differentiation between bacterial and viral etiologies. We evaluated the assay performance in URTI patients and compared it with standard laboratory measures.

METHODS

We performed a meta-analysis of 464 patients with clinical suspicion of URTI enrolled in three previously conducted multi-center clinical studies that evaluated the assay performance in patients with acute infections: 'Curiosity' study[1] (NCT01917461), 'Opportunity' study[2] (NCT01931254), and 'Pathfinder' study[3] (NCT01911143). Comparator method was based on expert panel adjudication, which was blinded to the test results. Diagnostic performance was evaluated by comparing test and comparator method outcomes.

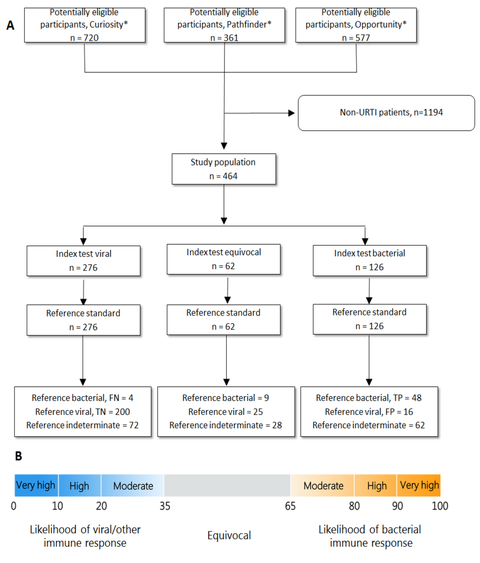
RESULTS

A unanimous panel adjudication was attained for 61 bacterial (13%) and 241 viral (52%) patients (162 patients (35%) had an indeterminate diagnosis). The assay distinguished between bacterial and viral infected patients with a sensitivity of 92% (95% CI: 82%- 98%) and specificity of 93% (88%-96%) with 11% equivocal test results. Overall the assay outperformed other routine laboratory tests, including: white blood cell count (WBC; cut-off 15,000 cells/µl, sensitivity 48% (35%-60%), $P<10^{-6}$; specificity 85% (80%-90%), P<0.05); CRP (cutoff 40 mg/L, sensitivity 82% (72%-92%), P=0.16, specificity 79% (74%-84%), $P<10^{-4}$;); Procalcitonin (PCT; cutoff 0.5 ng/ml, sensitivity 22% (11%-32%), $P<10^{-14}$), specificity 80% (74%-85%), P<0.001); absolute neutrophil count (ANC; cut-off 10,000 cells /µl, sensitivity 58% (45%-71%), $P<10^{-4}$; specificity 94% (91%-97%), P=0.7)..

CONCLUSIONS

The novel assay demonstrated superior performance compared to routine laboratory tests (WBC, ANC) and biomarkers (CRP, PCT), in distinguishing bacterial from viral etiologies in patients with URTI. It has the potential to help clinicians avoid missing bacterial infections or prescribing unwarranted antibiotics for viral URTIs.

Methods



A) Flow of participants through meta-analysis study. *Of note, the eligible participants for the meta-analysis are subsets of the original study cohorts, which included other subgroups less relevant in the current context (e.g. patients with non-infectious etiology). (B) ImmunoXpert™ test categories.

The meta-analysis involved pooling the data from three clinical studies: Curiosity[1] [n=1002], Opportunity[2] [n=777], and Pathfinder[3] [n=597].

For this meta-analysis, the participants of each study were included as potentially eligible if they met the respective study's inclusion and exclusion criteria. These potentially eligible participants were screened for the following additional inclusion criteria: clinical syndrome diagnosis of URTI by attending clinician at discharge (including pharyngitis, sinusitis, bronchitis, otitis and other URTI); aged ≥3 months, fever ≥38°C and symptom duration ≤6 days. Antibiotic treatment was not an exclusion criterion.

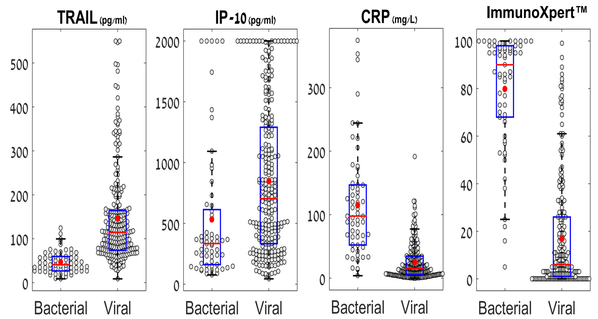
Patients who met one or more of the following criteria were excluded from the study: another infection episode during the last 3 weeks prior to sampling; congenital immune deficiency; proven or suspected HIV-1, HBV, HCV infection; active hematological malignancy; current treatment with immune-suppressive or immune-modulating therapies; other illnesses that affect life expectancy and/or quality of life.

Results

1. Baseline characteristics of URTI patients included in the meta-analysis

Characteristic	Study population (n=464)
Location of recruiting sites (n, %)	
Israel	413, 89%
Switzerland	13, 3%
Netherlands	38, 8%
Age (years) (mean, SD)	9.6 16.9
Gender, male (n, %)	260, 56%
Maximal temperature (°C) (mean, SD)	39.2, 0.8
Time from symptoms onset (days) (mean, SD)	3.2, 2.1
Hospital admission (n, %)	197, 42%
Hospitalization duration (days) (mean, SD)	1.3, 2.3
Antibiotic treatment prescribed (n, %)	240, 52%
Clinical syndrome (n, %)	
Pharyngitis	182, 39%
Sinusitis	4, 1%
Otitis	38, 8%
Bronchitis	29, 6%
Other URTI	211, 45%

2. The host proteins TRAIL, IP-10 and CRP and ImmunoXpert™ result (score) exhibit differential expression in bacterial and viral URTI patients

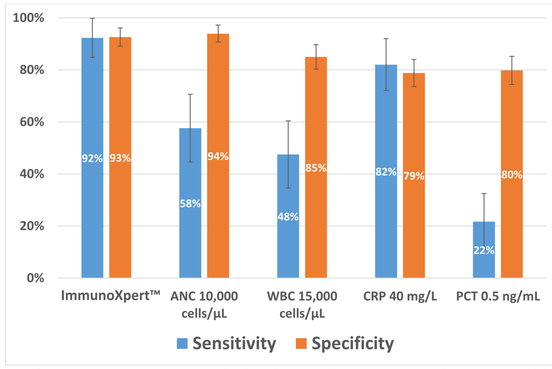


3. Diagnostic performance of ImmunoXpert™ for URTI patients included in meta-analysis

Accuracy measure	Assay performance (95% CI)*
Sensitivity	92.3% [81.5, 97.9]
Specificity	92.6% [88.3, 95.7]
PPV	75.0% [62.6, 85.0]
NPV	98.0% [95.1, 99.5]
LR +	12.46 [7.7, 20.1]
LR -	0.08 [0, 0.2]
DOR	150
Equivocal	11.3%

*Performance measures were calculated using the unanimous reference standard

4. ImmunoXpert™ outperforms WBC, ANC, CRP and PCT for URTI patients included in meta-analysis



Performance measures were calculated using the unanimous reference standard. ANC = Absolute neutrophil count; WBC = White blood cell count; CRP = C-reactive protein; PCT = procalcitonin

Discussion

Upper respiratory tract infections are the most common infectious diseases in the general population, estimated at 18 billion cases annualy[4]. Bacterial and viral URTIs are often clinically indistinguishable. This seemingly simple problem leads to antibiotic overuse, with detrimental ramifications for the patient, the healthcare system and society, including the emergence of antibiotic resistance. We describe a novel host-response based assay that can distinguish between bacterial and viral URTIs with sensitivity and specificity exceeding 90% and a negative predictive value of 98%. These findings, based on an extensive gender balanced study population of all ages with different URTI indications, from different countries, suggest the new assay may aid clinicians in the differential diagnosis of URTIs and help reduce antibiotic misuse.

References

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