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# Double-blind validation in febrile children of host-protein assay [TRAIL, IP-10, CRP] for distinguishing bacterial and viral infections

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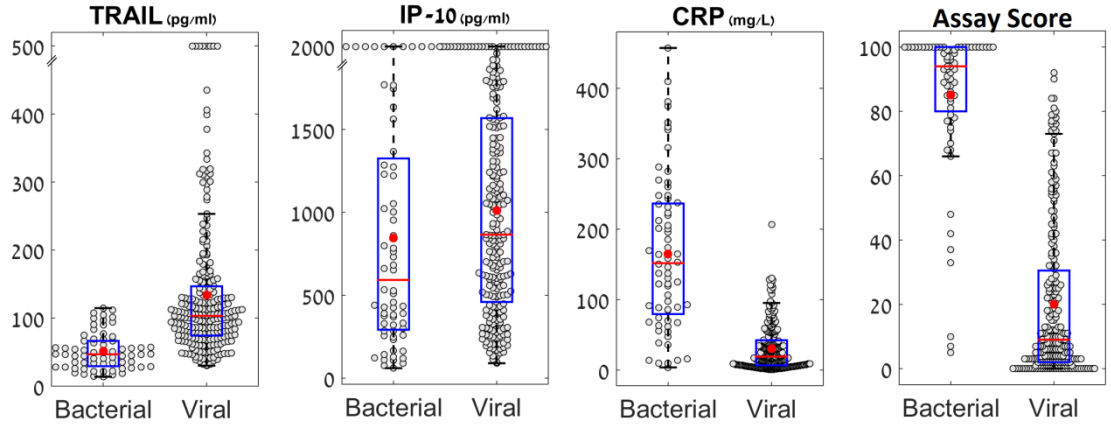
**Background:** Reliably distinguishing between bacterial and viral infections in febrile children is often challenging, leading to antibiotic misuse. A novel assay that integrates measurements of three blood-borne host-response proteins (TRAIL: TNF-realted apoptosis-inducing ligand; IP-10: Interferon gamma induced proten-10; CRP: C-reactive protein) was recently developed to assist in differentiation between bacterial and viral disease. We performed double-blind, multi-center assay evaluation.

**Material/methods:** Infectious and non-infectious children presenting to 5 pediatric emergency departments and inpatients aged ≥3 months to ≤18 years were retrospectively enrolled. Inclusion criteria for the infectious cohort were: suspicion of acute infection, fever ≥38°C, antibiotic treatment ≤48 hours and symptom duration ≤7 days. Reference standard diagnosis was based on predetermined criteria plus adjudication by an expert panel blinded to assay results. Assay performers were blinded to reference standard. Assay and routine parameter cutoffs were pre-defined before un-blinding.

**Results:** Of 597 potentially eligible patients, 56 were non-infectious, 101 did not fulfill infectious inclusion criteria and 79 had insufficient serum. The resulting infectious cohort comprised 361 patients: 239 viral, 68 bacterial, and 54 with indeterminate etiology. The infectious cohort was gender balanced (47% female), with average age of 4.1 years, and a wide range of temperatures, time from symptom onset, and clinical syndromes.

The levels of TRAIL and IP-10 were significantly higher in children with viral as compared to bacterial infections: mean (and standard deviation) levels of TRAIL were 139 (122) pg/ml vs. 52 (27) pg/ml, (P<0.001); and IP-10 levels were 1011 (626) ng/ml vs. 845 (677) ng/ml, (P<0.03), in agreement with previous studies. CRP exhibited the opposite pattern, with mean levels significantly lower in children with a viral infection: 31 (32) mg/L vs. 165 (108) mg/L, (P <0.001). The host-signature assay exhibited the most pronounced differential (P <0.001), with a mean viral patient score of 20 (24) as compared with 85 (23) in bacterial patients (Figure).

Figure: Differential expression of the host proteins TRAIL, IP-10, CRP and the host-signature assay score in children with bacterial and viral infections (n=307). Red line and circle correspond to group median and average respectively.




The assay distinguished between bacterial and viral infected patients with 93.8% sensitivity (95% CI: 87.8%-99.8%) and 89.8% specificity (85.6%-94.0%); 11.7% had an equivocal assay outcome. Assay outperformed other clinical parameters, including: (i) white blood count (cut-off 15,000cells/µl), sensitivity 72.7% (61.7-83.8), P<0.002; and specificity 83.2% (78.3-88.1), P<0.05); (ii) CRP (cutoff 40 mg/L), sensitivity 88.2% (80.4%-96.1%; P<0.37), specificity 73.2% (67.6%-78.9%; P<0.001); (iii) PCT (cutoff 0.5 ng/ml): sensitivity 63.1% (51.0%-75.1%; P<0.001), specificity 82.3% (77.1%-87.5%; P<0.03).

**Conclusions:** Assay performance was validated in febrile children in a double-blinded study. Assay was more accurate than CRP, PCT and routine clinical parameters. Additional studies are warranted to support its potential to improve antimicrobial treatment decisions.