ID WEEK 2015

A Novel Host-Protein Signature Outperforms Standard Laboratory Parameters in Differential Diagnosis of Acute Infection Etiology of Febrile Children

MeMed Diagnostics
+972-4-8500302
kfiroved@me-med.com

Kfir Oved[1], Asi Cohen[1], Olga Boico[1], Roy Navon[1], Tom Friedman[1,2], Liat Etshtein[1,2], Or Kriger[3], Ellen Bamberger[1,4,5], Yura Fonar[5], Renata Yacobov[3], Ron Wolchinsky[5], Galit Denkberg[6], Yaniv Dotan[4,5], Amit Hochberg[3], Yoram Reiter[5], Moti Grupper[4,5], Isaac Srugo[4,5], Paul Feigin[5], Malka Gorfine[5], Irina Chistyakov[4,5], Ron Dagan[7], Adi Klein[3], Israel Potasman[4,5], and Eran Eden[1]

[1]MeMed Diagnostics, Tirat Carmel, Israel, [2]Rambam Medical Center, Haifa, Israel, [3]Hillel Yaffe Medical Center, Hadera, Israel, [4]Bnai Zion Medical Center, Haifa, Israel, [5]Technion-Israel Institute of Technology, Haifa, Israel, [6]AIT, Haifa, Israel, [7]Soroka Medical Center, Beer-Sheva, Israel

Abstract

Background

We developed a novel immunoassay that distinguishes between bacterial and viral infections based on the patient's immune response (ImmunoXpert™). It combines both viral- and bacterial-induced host-proteins (TRAIL, IP-10 and CRP), and computes a bacterial likelihood score. Here we compare the assay performance with standard laboratory and clinical parameters that are routinely used in clinical practice to facilitate diagnosis of infection etiology in febrile children.

Methods

We studied 272 febrile children (3 months to 18 years) with bacterial or viral etiologies, as determined by unanimous agreement of three independent physicians following comprehensive clinical and laboratory investigation (physical examination, medical history, complete blood, chemistry panel and a multiplex PCR panel applied on nasal swabs [Seeplex RV15 and PB6]). A bacterial likelihood score was computed for each patient using the serum levels of the three host-proteins[1], and compared to the reference standard diagnosis[2-4].

Results

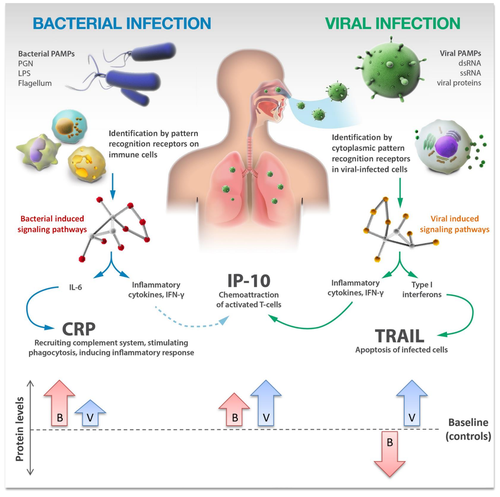
Expert panel diagnosis yielded 80 bacterial and 192 viral diagnoses. The assay had a sensitivity of 0.93±0.06 and specificity of 0.95±0.03 for differentiating between bacterial (or mixed bacterial and viral co-infection) and viral infections (29 patients had equivocal test results). It outperformed routinely-used clinical parameters when applying routinely used cutoffs including white blood cell count (WBC, sensitivity 0.62±0.09, specificity 0.83±0.05; 15,000/µl cutoff;), absolute neutrophil count (ANC, sensitivity 0.67±0.1, specificity 0.85±0.05; 10,000/µl cutoff), maximal temperature (sensitivity 0.34±0.1; specificity 0.74±0.06; 40ºC/104ºF cutoff), and CRP (sensitivity 0.9±0.07; specificity 0.59±0.05; 20 µg/ml cutoff, and sensitivity 0.56±0.09, specificity 0.96±0.06; 80 µg/ml cutoff). Different combinations of WBC, ANC and CRP yielded lower sensitivity (0.39-0.61) and similar specificity (0.90-0.99), compared to the evaluated assay.

Conclusions

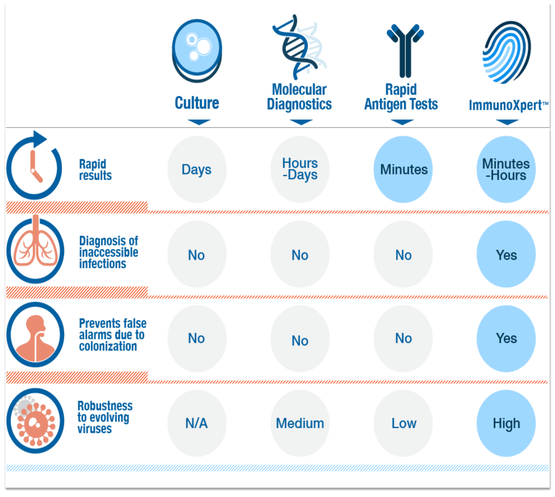
The host response-based assay outperformed WBC, ANC, temperature and CRP in differentiating between bacterial (or mixed) versus pure viral etiologies. It has the potential to improve the management and health outcome of febrile children.

Discussion

Bacteria and viruses stimulate different immune-pathways



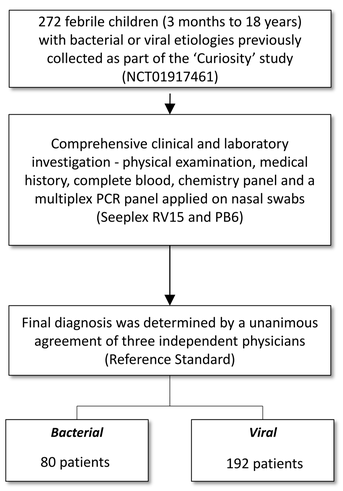
New assay overcomes limitations of current diagnostics



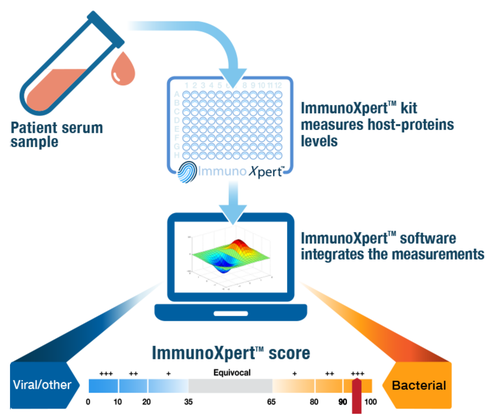
Despite advances in infectious disease diagnosis, timely identification of bacterial infections remains challenging, leading to antibiotic misuse with its profound health and economic consequences. To address the need for better treatment guidance, we previously developed and validated a signature that combines novel and traditional host-proteins for differentiating between bacterial and viral infections[1]. A kit called ImmunoXpert™ was developed, which measures the proteins in 99 minutes using an ELISA format, and computationally integrates the measurements into the final diagnosis. The new assay provides valuable information over standard laboratory and clinical parameters and addresses several distinct challenges of current microbiological testing. It has the potential to improve the management of patients with acute infections and reduce antibiotic misuse.

Methods and Results

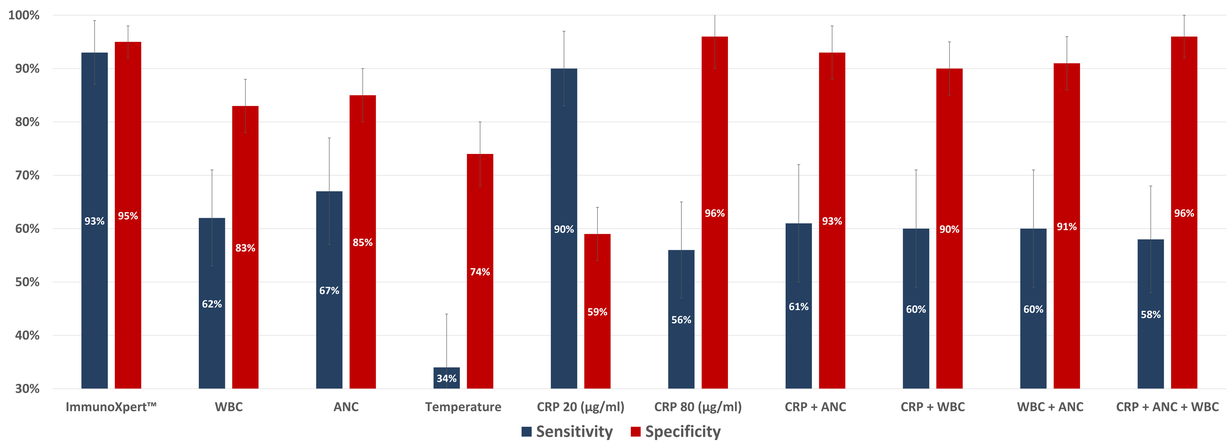
Study design



Assay principles



New assay outperformed routine clinical parameters and their combinations



ImmunoXpert™ assay outperformed routinely-used clinical parameters when applying routinely used cutoffs such as white blood cell count (WBC, 15,000/µl cutoff), absolute neutrophil count (ANC, 10,000/µl cutoff), maximal temperature (40ºC/104ºF cutoff), and CRP (20 µg/ml and 80 µg/ml cutoffs). Different combinations of WBC, ANC and CRP (20 µg/ml) yielded lower sensitivity and similar specificity, compared to the evaluated assay

References

1. Oved, K. et al. A Novel Host-Proteome Signature for Distinguishing between Acute Bacterial and Viral Infections. PLoS ONE 10, e0120012 (2015)
2. Bertens LCM, et al. Use of expert panels to define the reference standard in diagnostic research: a systematic review of published methods and reporting. *PLoS Med*. (2013)
3. Bossuyt PM, et al. The STARD Statement for Reporting Studies of Diagnostic Accuracy: Explanation and Elaboration. *Ann Intern Med* (2003)
4. Rutjes AWS, et al. Evaluation of diagnostic tests when there is no gold standard. A review of methods. *Health Technol. Assess. Winch. Engl*. (2007)

MeMed