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TNF-related apoptosis-inducing ligand (TRAIL) protein as a biomarker for viral infections in febrile children

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Background: A major challenge in effective management of febrile patients, especially children, is the clinical difficulty of distinguishing between bacterial and viral infections. Bacterial-induced host proteins such as procalcitonin, C-reactive protein, and Interleukin-6, are routinely used to support diagnosis of infection. However, their performance is negatively affected by inter-patient variability. One approach to improving performance is to evaluate also viral-induced biomarkers. TRAIL is a member of the tumor necrosis factor family implicated in programmed cell death. We recently demonstrated that TRAIL can serve as a useful biomarker for distinguishing between bacterial and viral infections when computationally combined with CRP and IP-10 (ImmunoXpert™ signature; Oved et al. 2015). Here we evaluate TRAIL levels in children with various viral infections as well as in bacterially infected children and controls.

Material/methods: We studied 233 febrile children and 15 non-infectious controls. Patient etiology (78 bacterial and 155 viral) was determined by majority adjudication of three physicians based on comprehensive clinical and laboratory investigation. Bacterial and viral strains were detected using multiplex-PCR applied to nasal swabs [Seeplex-RV15/PB6]). Serum TRAIL levels were measured using ELISA (MeMed).

Results: TRAIL levels were increased in viral patients and decreased in bacterial patients (average±SD [pg/ml]: bacterial 44±32; viral 153±110; controls 78±29; Figure-1). Among the 11 viral types evaluated, Influenza A and B induced the highest TRAIL elevation (206±113 and 253±194 pg/ml respectively), while adenovirus induced the lowest (98±41 pg/ml; Figure 1). The difference between TRAIL levels in viral and bacterial patients was statistically significant for all evaluated strains (ttest p-value<0.001).

Conclusions: TRAIL expression increases in patients infected with a wide range of viral strains. Elevations in TRAIL expression may assist in inhibiting virus spread by promoting apoptosis of infected cells. While induction of TRAIL levels in response to viral disease was statistically significant for all viral strains examined, some strain specific variability was observed. For example, Influenza disease, which manifests as an acute febrile illness with variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death, induced the highest TRAIL elevation. In contrast, Adenovirus, which is known to trigger a bacterial-like inflammatory host response with clinical manifestation including prolonged fevers, leukocytosis and elevated CRP, exhibited the lowest induction. Although TRAIL is induced less by adenovirus, the opposing dynamics of TRAIL in response to bacterial versus viral infections may assist in distinguishing between adenovirus and bacterial infections that induce similar clinical symptoms. Taken together, our findings highlight TRAIL as a potentially valuable biomarker for assisting in correct management of febrile children.

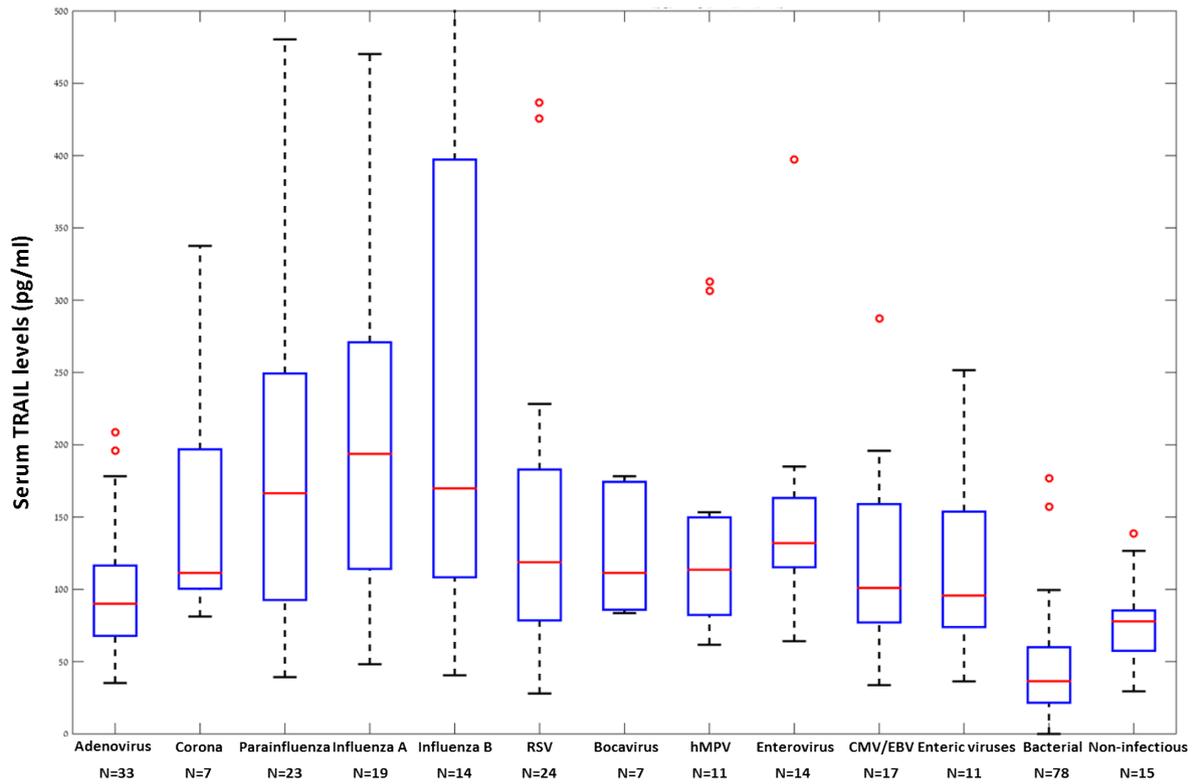


Figure1. Serum TRAIL levels of patients presenting with different infection types

First-to- third quartiles (boxes) and median (red line) are presented. RSV-Respiratory syncytial virus; hMPV–human Metapneumovirus; Enteric viruses: Rota Virus, Astrovirus, Enteric Adenovirus, Norovirus.