A Host-Response Signature Based on TRAIL, IP-10 and CRP Addresses Antibiotic Misuse Driven by Diagnostic Uncertainty

Background:
Children arriving to the emergency department with fever without source (FWS) or respiratory tract infection (RTI) often present a diagnostic challenge. Here we evaluated whether clinical uncertainty drives antibiotic misuse and if a novel host-response signature comprising TRAIL, IP-10, CRP (MeMed Ltd) that distinguishes viral from bacterial infection could potentially reduce uncertainty, improve diagnostic accuracy and support better informed antibiotic decisions.

Methods:
We performed multinational prospective evaluation at pediatric emergency departments (ED) in Germany and Italy (“AutoPilot-Dx”; grant #701088). Infection etiology was determined by unanimous decision of 3 independent experts. Managing ED physicians were asked to estimate their certainty if the patient had a viral or bacterial infection. Association between clinical uncertainty and antibiotic misuse was evaluated. The signature outputs a score between 0 and 100, accorded 5 score bins. Diagnostic performance of the signature vs managing physician was assessed across all patients and those with diagnostic uncertainty, according to pre-determined cutoffs.

Results:
A total of 732 children were included in the final analysis cohort (628 viral, 104 bacterial). Managing physicians reported diagnostic uncertainty for 537 of the 732 patients (73%). Overuse and underuse antibiotic rates were higher in the uncertain as compared to certain sub-cohort (34.0% vs 16.8%, 10.0% vs 5.9%, respectively). The likelihood ratio for bacterial infections exhibited a significantly increasing trend with score (P<0.001; figure 1). A potential reduction in antibiotic overuse of 3.3-fold (from 30% to 9%) and underuse of 1.3-fold (9% to 7%) was observed. In the uncertain sub-cohort, the potential reduction in antibiotic overuse and underuse was higher at 3.8-fold (34% to 9%) and 1.7-fold (10% to 6%), respectively.

Conclusions:
ED physician diagnostic uncertainty drives antibiotic misuse among children with RTI or FWS. The TRAIL/IP-10/CRP signature shows high performance for distinguishing between bacterial and viral infections, especially for patients with diagnostic uncertainty, and may help reduce antibiotic misuse.

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**Figure 1.** The likelihood ratio (LR) for bacterial infection increases as the score increases (A).

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