

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



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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.

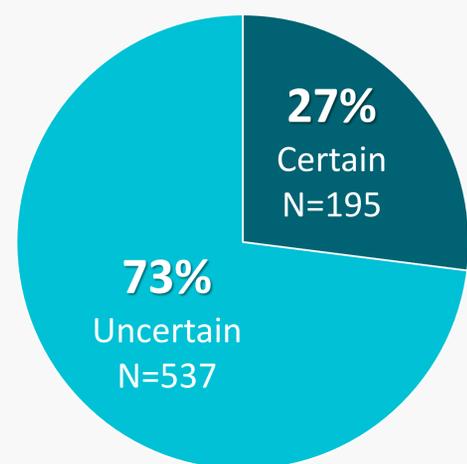
Results:

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.

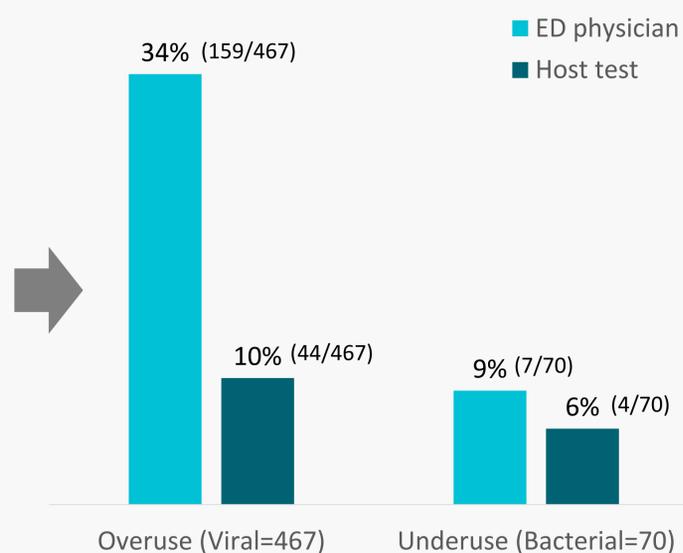
Conclusions:

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.

ED Physician diagnostic certainty N=732



Potential impact on antibiotic misuse Uncertain patients N=537



Bacterial or Viral infection (N=732)

Score Bin	Patients n(%)	Bacterial n(%)	Viral n(%)	LR (90% CI)
90 ≤ score ≤ 100	77 (10.5)	73 (94.8)	4 (5.2)	110.20 (40.71-298.28)
65 ≤ score ≤ 90	45 (6.1)	16 (35.6)	29 (64.4)	3.33 (1.84-6.03)
35 ≤ score ≤ 65	72 (9.8)	9 (12.5)	63 (87.5)	0.86 (0.44-7.71)
10 ≤ score ≤ 35	151 (20.6)	4 (2.6)	147 (97.4)	0.16 (0.06-0.44)
0 ≤ score ≤ 10	387 (52.9)	2 (0.5)	385 (99.5)	0.03 (0.01-0.12)
Total	100	104	628	

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

ED managing physician overuse and underuse rates were compared to those of the signature across patients about whom the ED managing physician was clinically uncertain (B). ED physician overuse was defined as viral patients receiving antibiotics, underuse as bacterial patients not receiving antibiotics or receiving delayed treatment. The signature's potential misguidance of treatment was defined according to pre-defined CE-IVD cutoffs: overuse was viral patients with a score over 65, indicative of a bacterial infection (false positives), underuse as bacterial patients with a score under 35, indicative of viral infection (false negatives). Equivocal results corresponding to scores 35-65 do not provide diagnostic information and so potential antibiotic misguidance in these cases was defined according to the ED physician's treatment.