BV Score (based on TRAIL, IP-10 and CRP) Accurately Distinguishes Between Bacterial and Viral Infection in Febrile Children: A Multi-Cohort Analysis

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Abstract

Background:

BV is a score for differentiating between bacterial and viral etiologies. Recently FDA cleared, it is based on computational integration of the blood levels of three host-proteins (TRAIL, IP-10, CRP). Here we report a multi-cohort analysis validating its diagnostic performance against a microbiology confirmed reference standard for children recruited in the Netherlands, Germany, Italy, Israel and the United States.

Methods:

Febrile pediatric patients (aged < 18) were recruited at the Emergency Department and Urgent Care Centers in the Apollo (NCT04690569), Autopilot (NCT03052088) and Opportunity (NCT01931254) studies. Eligibility criteria included suspicion of acute bacterial or viral infection symptoms for < 7 days and immunocompetence. Three experts independently reviewed comprehensive patient data including follow-up data but were blinded to BV. A bacterial or viral microbiology confirmed reference standard required all 3 experts to assign the same etiology and also a positive microbiology result supporting the experts' decision (Figure legend). BV is indicative of bacterial or viral infection (MeMed BV®) based on pre-defined thresholds: 0 ≤ score < 35 indicates viral (or other non-bacterial) infection, 35 ≤ score ≤ 65 indicates equivocal and 65 < score ≤ 100 indicates bacterial infection (or co-infection). BV performance was assessed against the reference standard.

Results:

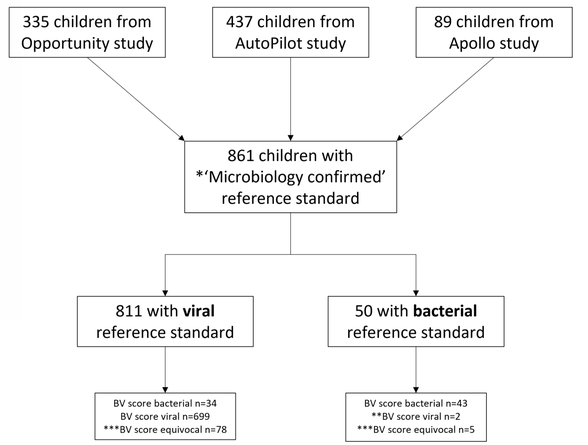
Among the 1,747 children recruited in the 3 studies, 861 were assigned a microbiology confirmed reference standard, with 811 viral and 50 bacterial cases (bacterial prevalence 6%). The median age was 1.8 years (interquartile range: 0.9-3.5 years), 42.3% were female, and 72.7% were diagnosed with respiratory tract infection or unspecified viral infection. BV yielded sensitivity and specificity of 95.6% (95% confidence interval: 84.9%-99.5%) and 95.4% (95%CI: 93.6%-96.8%), and negative predictive value of 99.7% (95%CI: 98.9%-99.9%), with 9.6% of cases yielding equivocal scores.

Conclusion:

BV accurately distinguishes bacterial from viral infection in microbiology confirmed cases and has potential to support etiological diagnosis in children presenting to acute care settings.

Figure 1. FDA Cleared BV test

Figure 2. Patient Enrollment Flow



*'Microbiology confirmed' reference standard required a unanimous expert panel diagnosis and in addition, at least one of the following: blood culture positive for a pathogen; cerebrospinal culture positive for a pathogen; positive urine culture with ≥50,000 CFU/mL (a pathogen) and leukocytes and/or nitrite positive urine; a positive throat culture with Group A/C/G Streptococcus; a peritonsillar abscess proven by surgical exploration or computerized tomography; or viral detection.
**Case 1: A 1-year-old child presented with rhinorrhea, fatigue, anorexia, and fever; by clinical examination well appearing, rash and stomatitis; not hospitalized. Blood culture: *Kingella kingae*; nasal swab: enterovirus and bocavirus.
Case 2: A 10-years-old child presented fever and decreased solid intake; normal clinical examination; ultrasound of the kidney showed hydronephrosis sediment: high concentration of leukocytes; absence of nitrite. Urine culture: *Escherichia coli* >10^5 colony forming units per mL.
***Equivocal scores represent valid test results but do not provide etiological information, and they are removed from test performance calculations.

Table 1. Discharge diagnoses

*Viral reference standard	# Cases
URTI Unspecified	203
Viral infection unspecified	129
Fever Without a Source	100
Bronchiolitis	74
Pneumonia	63
Acute Bronchitis	48
Other Unspecified	46
Tonsillitis/Pharyngitis	31
LRTI Unspecified	27
URTI - Other	17
Other	16
Acute Otitis Media	15
Gastroenteritis/Abdominal pain	13

*10 cases and above

Bacterial reference standard	# Cases
UTI	30
Tonsillitis/Pharyngitis	8
Pneumonia	4
Bacteremia	3
Fever Without a Source	1
Other Unspecified	1
Acute Otitis Media	1
CNS	1
Abscess	1

Table 2. Pathogens**

Viral reference standard	# Cases
Rhinovirus/Enterovirus	325
Influenza	210
Respiratory syncytial virus	166
Adenovirus	128
Bocavirus	72
Parainfluenza	69
Human Metapneumovirus	68
Coronavirus	47
EBV/CMV	14
Group A streptococcus	1

Bacterial reference standard	# Cases
E.coli	27
Rhinovirus/Enterovirus	14
Group A streptococcus	9
Adenovirus	5
Parainfluenza	5
Respiratory syncytial virus	4
Bocavirus	3
Coronavirus	3
Influenza	1
EBV/CMV	1

**Patients may have more than 1 pathogen detected. For example, 23 cases in the bacterial reference standard had a viral co-detection. Detection methods were routine care plus a study-specific nasopharyngeal PCR panel.

Background

BV is a score for differentiating between bacterial and viral etiologies. It is based on computational integration of the blood levels of three host-proteins (tumor necrosis factor-related apoptosis-inducing ligand [TRAIL], interferon gamma-induced protein-10 [IP-10], CRP). Here we report a multi-cohort analysis validating its diagnostic performance in comparison to a microbiology confirmed reference standard for children recruited in the Netherlands, Germany, Italy, Israel and the United States.

Methods

Febrile pediatric patients (age: 3 months to 18 years old) were recruited in Emergency Departments and Urgent Care Centers in the Apollo (NCT04690569), AutoPilot (NCT03052088) and Opportunity (NCT01931254) studies. Eligibility criteria included suspicion of acute bacterial or viral infection, with symptoms for < 7 days in patients deemed to be immunocompetent. BV is indicative of bacterial or viral infection according to pre-defined thresholds: 0 ≤ score < 35 indicates viral (or other non-bacterial) infection, 35 ≤ score ≤ 65 indicates equivocal and 65 < score ≤ 100 indicates bacterial infection (or co-infection). BV was measured using an ELISA platform (ImmunoXpert™) for the Opportunity and AutoPilot studies and using a point-of-need platform (MeMed BV® run on MeMed Key®, Figure 1) for the Apollo study; comparability of results from the two platforms has been established. BV performance was assessed against a reference standard. Three experts independently reviewed comprehensive patient data including follow-up data but were blinded to BV. A bacterial or viral microbiology confirmed reference standard required all 3 experts to assign the same etiology in addition to a positive microbiology result supporting the experts' decision (Figure 2 legend).

Results

Among the 1,747 children recruited in the 3 studies, 861 were assigned a microbiology confirmed reference standard, with 811 viral and 50 bacterial cases (bacterial prevalence 6%; Figure 2). The median age was 1.8 years (interquartile range: 0.9-3.5 years), 42.3% were female, and 72.7% were diagnosed with respiratory tract infection or unspecified viral infection. Discharge diagnoses and Pathogens are shown in Tables 1 and 2, respectively. BV yielded sensitivity and specificity of 95.6% (95% confidence interval: 84.9%-99.5%) and 95.4% (95%CI: 93.6%-96.8%), and negative predictive value of 99.7% (95%CI: 98.9%-99.9%), with 9.6% of cases yielding equivocal scores.

Conclusion

BV accurately distinguishes bacterial from viral etiology in microbiology confirmed cases in febrile non-immunocompromised children 3 months to 18 years of age and has the potential to support clinical diagnosis in febrile children presenting to acute care settings.