

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.

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).

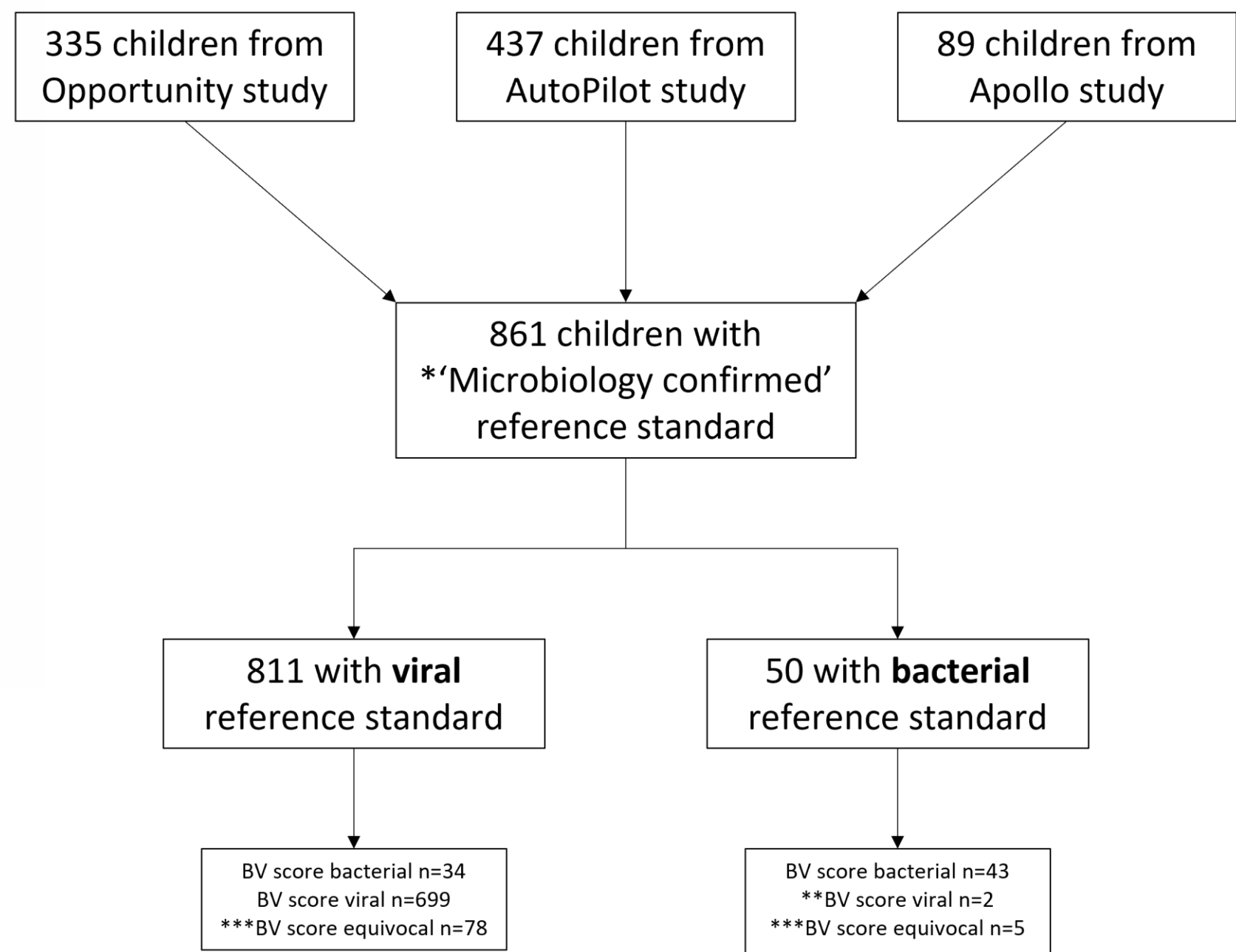
Results

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.

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* >10⁵ 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	Bacterial reference standard	# Cases
URTI Unspecified	203	UTI	30
Viral infection unspecified	129	Tonsillitis/Pharyngitis	8
Fever Without a Source	100	Pneumonia	4
Bronchiolitis	74	Bacteremia	3
Pneumonia	63	Fever Without a Source	1
Acute Bronchitis	48	Other Unspecified	1
Other Unspecified	46	Acute Otitis Media	1
Tonsillitis/Pharyngitis	31	CNS	1
LRTI Unspecified	27	Abscess	1
URTI - Other	17		
Other	16		
Acute Otitis Media	15		
Gastroenteritis/Abdominal pain	13		
*10 cases and above			

Table 2. Pathogens**

Viral reference standard	# Cases	Bacterial reference standard	# Cases
Rhinovirus/Enterovirus	325	<i>E. coli</i>	27
Influenza	210	Rhinovirus/Enterovirus	14
Respiratory syncytial virus	166	Group A streptococcus	9
Adenovirus	128	Adenovirus	5
Bocavirus	72	Parainfluenza	5
Parainfluenza	69	Respiratory syncytial virus	4
Human Metapneumovirus	68	Bocavirus	3
Coronavirus	47	Coronavirus	3
EBV/CMV	14	Influenza	1
Group A streptococcus	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.			

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.