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Rapid identification of nonblood sterile site broth cultures using the FilmArray blood culture identification panel

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ABSTRACT

The FilmArray Blood Culture Identification Panel was validated for nonblood sterile site specimens with clinical impact of rapid identification compared to conventional diagnostics. The panel accurately identified target organisms from 98% of positive broth cultures a median 1.1 day faster than conventional techniques ($P < 0.0001$) with potential clinical impact in 22% of cases.

Rapid organism identification from positive blood cultures using multiplex polymerase chain reaction (PCR) assays, such as the FilmArray Blood Culture Identification Panel (BCID; BioMérieux, France), has been associated with optimized use of antimicrobials and improved patient outcomes (Messacar et al., 2017; Timbrook et al., 2017). Cultures from sterile sites other than blood and cerebrospinal fluid (CSF) rely upon culture growth on solid media for conventional microbiologic identification. Despite being designed and FDA-approved for identification of blood culture specimens (Blaschke et al., 2012), the targets included on the BCID panel are pertinent to sterile body site infections grown in broth culture. Though previous studies have validated the use of BCID on nonblood sterile site specimens (Altun et al., 2015; Micó et al., 2015), the validity and potential clinical impact of this testing in pediatric populations are unknown.

This was a 2-part, analytical and clinical, validation study testing deidentified specimens using a protocol approved by the Colorado Multiple Institutional Review Board. For the analytical validation, 3 pathogen pools encompassing organisms on the BCID panel were spiked into source specimens (bone, synovial fluid, shunt fluid, pleural fluid, tissue, and abscesses) created from pooled residual patient specimens to account for matrix interferences. Negative controls were prepared from each source pool and inoculated into blood culture bottles without organisms. The clinical validation was performed by prospectively testing positive broth cultures from sterile site specimens. These positive broth cultures were inoculated BD Peds Plus blood culture bottles that flagged positive on the Bactec FX (Bectin Dickinson, Heidelberg, Germany). Positive broth bottles were also cultured in parallel on solid media with conventional microbiologic identification (Supplementary Methods). Agreement between organisms identified by BCID and culture was calculated for BCID targets with non-BCID target organisms grown in culture noted separately. Time-to-identification was calculated from the time of specimen collection to organism identification using conventional techniques and compared to the expected turnaround for BCID (2 h after broth culture flagged on BD Bactec FX). As previously described (Messacar et al., 2017), time-to-effective antimicrobials was defined as time from specimen collection to first dose of an antimicrobial to which the cultured organisms tested as susceptible, and time-to-optimal antimicrobials was defined as time from specimen collection to first dose of predefined targeted antimicrobial therapy based on expert review (KM and SRD). Cases in which a patient was not on effective or optimal antimicrobials at the time of BCID result were identified with the potential change in time to these outcomes recalculated as if the BCID result were available. These cases were compared to all tested in order to identify the subset of patients for which this testing may have had clinical impact. Medians for continuous

Abbreviations: PCR, polymerase chain reaction; BCID, FilmArray Blood Culture Identification Panel; CSF, cerebrospinal fluid.

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Table 1
Accuracy and potential clinical impact of the FilmArray blood culture identification panel for sterile site broth culture specimens.

Specimen type	Number of specimens	BCID accurate for all target organisms (% agreement)	Potential for clinical impact of BCID testing[a] (%)
Bone biopsy	19	18 (95%)	3 (15.8%)
Tissue biopsy	15	15 (100%)	3 (20%)
Lymph node aspirate	15	15 (100%)	2 (13.7%)
Abscess/cellulitis aspirate	14	14 (100%)	1 (7.1%)
Cerebrospinal fluid from ventriculoperitoneal shunt	15	15 (100%)	7 (46.7%)
Peritoneal/dialysate fluid	5	4 (80%)	1 (20%)
Pleural fluid	4	4 (100%)	2 (50%)
Synovial fluid	3	3 (100%)	1 (33.3%)
TOTAL	**90**	**88 (98%)**	**20 (22.2%)**

[a] Includes potential decreased time-to-effective or time-to-optimal antimicrobials.

variables were compared using Wilcoxon rank sum test with statistical significance set at $\alpha = 0.05$.

For the analytical validation, all targets from organism pools were detected from all source pools, and negative pools had no targets detected (100% sensitivity, 100% specificity). For the clinical validation, 90 positive broth cultures, including bone biopsy (19), tissue biopsy (15), lymph node aspirate (15), CSF from shunt (15), abscess/cellulitis aspirate (14), peritoneal/dialysate fluid (5), pleural fluid (4), and joint fluid (3), were included (Table 1). BCID was 97% consistent with conventional identification of target organisms with 2 discordant results: a *Staphylococcus simulans* in polymicrobial culture from a decubitus ulcer osteomyelitis was identified as methicillin-resistant *Staphylococcus aureus* (MRSA), and a *Citrobacter* sp. in polymicrobial culture from peritonitis was identified as *Enterobacter cloacae* complex (Supplementary Table). Two samples were reported as MRSA on BCID due to the detection of *Staphylococcus aureus* and *mecA* targets, but the cultures were positive for methicillin-susceptible *S. aureus* (MSSA) and oxacillin-resistant coagulase-negative *Staphylococcus*. Thirteen organisms grew in culture that were not BCID targets. The median time-to-identification was 1.1 days faster with BCID than conventional identification (0.82 days vs. 1.92 days; $P < 0.0001$).

BCID could have led to more rapid time-to-effective antimicrobials in 10 cases (11%), a median of 1.18 days faster than conventional techniques (0.77 vs. 1.95; $P < 0.0001$). The most common changes in effective antimicrobials would have been adding coverage for Gram-negative organisms with inducible beta-lactamase resistance mechanisms ($n = 7$). More rapid time-to-optimal antimicrobials could have been possible with BCID in 20 cases (22%), a median of 1.26 days faster (0.74 vs. 2.0; $P = 0.0005$). The most common change in optimization of antimicrobials would have been more rapid discontinuation of vancomycin for MSSA ($n = 6$), discontinuation of antimicrobials for likely contaminants ($n = 3$), and narrowed antifungal coverage for yeast ($n = 2$). The specimen types tested by BCID that were most likely to be clinically impactful were pleural fluid, CSF from shunts, and synovial fluids.

This study suggests that BCID can provide accurate and rapid identification of organisms from cultures of sterile bodily fluid specimens in children with the potential to improve clinical outcomes through earlier optimization of antimicrobial regimens. Previous studies have demonstrated comparable sensitivity and specificity of BCID for sterile site specimens (Altun et al., 2015) and clinical impact in case reports (Michos et al., 2016; Pardo et al., 2014); however, this is the first systematic assessment of potential clinical impact in pediatric populations. Though multiplex PCR platforms are now FDA-approved for respiratory, stool, CSF, and blood specimens, there remains a need for more rapid identification of other sterile site specimens. The BCID panel of organisms fulfills this need, particularly for musculoskeletal, pleural, and shunt specimens in pediatric patients.

This study carries inherent limitations due to its retrospective nature. While potential clinical impact was calculated in an ideal setting where appropriate clinical action would be taken at the time of test result, in the real world, this response may be delayed or suboptimal without the involvement of active antimicrobial stewardship real-time decision support (Messacar et al., 2017).

In summary, the FilmArray BCID system can identify organisms in positive sterile site broth cultures from pediatric patients with excellent sensitivity and specificity while significantly decreasing time-to-organism-identification. Caution must be taken in the interpretation of results from specimens likely to contain polymicrobial infections due to decreased sensitivity and organism detection limited to included targets. This panel cannot accurately distinguish MRSA when mixed cultures of MSSA and coagulase-negative, mecA-encoding staphylococci are analyzed. Our study suggests potential improvements in clinical outcomes with implementation of this assay. Further prospective studies are needed with effective implementation partnered with antimicrobial stewardship intervention strategies to evaluate cost-effectiveness and clinical impact in the real clinical environment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2018.07.018.

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