ORIGINAL ARTICLE

Clinical Utility of Blood Culture Identification 2 Panel in Flagged Blood Culture Samples from the Intensive Care Unit of a Tertiary Care Hospital

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Abstract

Background: The availability of rapid diagnostic platforms for positive blood cultures has accelerated the speed at which the clinical microbiology laboratory can identify the causative organism and facilitate early appropriate antimicrobial therapy. There is a paucity of data regarding the clinical utility of the blood culture identification 2 (BCID2) panel test and its correlation with phenotypic drug susceptibility testing (DST) in flagged blood culture bottles from intensive care units (ICUs) in countries such as India, which have high rates of multidrug-resistant gram-negative bacteria (MDR-GNB).

Materials and methods: We conducted a retrospective observational study in a tertiary care ICU on 200 patients above 18 years of age in whom a BCID2 test was ordered when blood cultures flagged positive.

Results: We found 99% concordance between BCID2 and cultures in the identification of bacteria and yeasts and 96.5% concordance between phenotypic and genotypic DST. Furthermore, BCID2 was available about 1.5 days earlier than conventional ID and DST and played a key role in tailoring antimicrobials in 82.5% of the patients. Polymyxin-based therapy was discontinued earlier after an empiric dose in 138 patients (69%) based on BCID2 reports.

Conclusion: In critically ill patients with monomicrobial bacteremia, BCID2 rapidly identifies bacteria and antimicrobial resistance (AMR) genes and is significantly faster than conventional culture and sensitivity testing. Antibiotics were escalated in more than a third of patients and de-escalated in almost a fifth on the same day. We recommend that all ICUs routinely incorporate the test in their antibiotic decision-making process and in antimicrobial stewardship.

Keywords: Antimicrobial stewardship, Blood culture identification 2, Flagged cultures, Polymyxin.

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Highlights

The availability of rapid diagnostic platforms for positive blood cultures has accelerated the speed at which the clinical microbiology laboratory can identify the causative organism and facilitate early appropriate antimicrobial therapy. In critically ill patients with bacteremia, BCID2 rapidly identifies microbes and antimicrobial resistance (AMR) genes and is much faster than conventional culture and sensitivity testing. This panel provides rapid results that will guide appropriate same-day management of empirical antimicrobial therapy in a large proportion of patients with bacteremia.

Introduction

Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection.[1] Identifying early and adequate management in the initial hours after the development of sepsis improves outcomes.[2] Initiating early appropriate antibiotics in sepsis plays a major role in avoiding complications, strengthening antimicrobial stewardship, and slowing antimicrobial resistance (AMR).

The rapid diagnostic platforms for positive blood cultures have quickened the turnaround time at which microbiology laboratories can identify the causative microbe to facilitate early appropriate antimicrobial therapy.[3] Blood culture identification 2 (BCID2) panel test is a US Food and Drug Administration (FDA)-cleared, nucleic acid amplification and detection assay FilmArray that identifies

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43 targets—11 gram-positive targets, 15 gram-negative targets, 6 *Candida* species, 1 *Cryptococcus* species, and multiple antibiotic resistance genes as depicted in Table 1.[4] The test can be completed in 1 hour 4 minutes.

The sensitivity across all pathogens on the BCID2 panel is 99%, and the specificity is 99.8%.[4] There is a paucity of data regarding the utility of BCID2 in antimicrobial stewardship and its correlation with phenotypic drug susceptibility testing (DST) in flagged blood culture bottles from intensive care units (ICUs) in countries such as India, which have high rates of MDR GNB.[5] We studied the clinical and microbiological profile of patients who underwent BCID2 panel testing on flagged blood samples in a tertiary care hospital setting and analyzed how antibiotics were escalated or de-escalated based on BCID2 prior to the information available through routine microbiological methods.

Materials and Methods

We conducted a retrospective observational study in a tertiary care ICU from August 2021 to June 2022, focusing on patients aged 18 and above. This study was undertaken after approval from the Institutional Ethical Committee (IEC). We included patients for whom a BCID2 test was ordered upon positive blood culture flagging and detection of bacteria or yeast on smear examination. Only one episode of bacteremia per patient was considered. We analyzed case records for demographic, clinical, and microbiological information. Sepsis was defined according to 2021 Surviving Sepsis guidelines.[1]

Clinical data considered were probable sources of sepsis according to case records, national early warning score 2 (NEWS 2) based vital signs; a number of flagged blood culture bottles, the profile of bacteremia, smear findings of flagged culture bottles, AMR targets and microbial targets, concordance of genotypic identification with phenotype were checked. Run out time of BCID2 was the time duration between flagging of blood culture and availability of report of BCID2. Run-out time for culture was the duration between the flagging of blood culture and the availability of identification and sensitivity report. The mean and median of both run-out times were calculated. Descriptive statistical analysis was done using mean, frequency, and percentages.

Blood Culture Protocol

The blood culture procedure involved using the BacT/ALERT system by Biomerieux. Upon flagging, a Gram stain of the sample was performed, and the results were communicated to the physician *via* telephone. Subsequently, colonies were subcultured and identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI TOF MS). Drug susceptibility testing was conducted using a combination of methods, including VITEK by Biomerieux and the Kirby Bauer disk diffusion method, following the guidelines outlined by the Clinical Laboratory Standards Institute (CLSI) for 2021–2022.[6]

Blood Culture Identification 2 Protocol

The BioFire BCID2 Panel pouch serves as a sealed disposable system housing all essential reagents for sample preparation, polymerase chain reaction (PCR), and detection. It is designed to isolate, amplify, and detect nucleic acid from various pathogens and AMR genes present in blood culture samples flagged as positive by a continuous monitoring blood culture system. Following sample collection, the user adds hydration solution and combines it with the sample in the sample buffer, then inserts the pouch into a BioFire FilmArray instrument module and begins the test.

Table 1: Blood culture identification 2 targets

The BioFire BCID2 panel targets		
Gram-negative bacteria	*Gram-positive bacteria*	*Antimicrobial resistance genes*
Acinetobacter calcoaceticus–Acinetobacter baumannii complex	*Enterococcus faecalis*	*Carbapenemases*
Bacteroides fragilis	*Enterococcus faecium*	*IMP*
Enterobacterales	*Listeria monocytogenes*	*KPC*
Enterobacter cloacae complex	*Staphylococcus* species	*OXA-48-like*
E. coli	*Staphylococcus aureus*	*NDM*
Klebsiella aerogenes	*Staphylococcus epidermidis*	*VIM*
Klebsiella oxytoca	*Staphylococcus lugdunensis*	Colistin resistance
K. pneumoniae group	*Streptococcus* species	*mcr-1*
Proteus species	*Streptococcus agalactiae*	*ESBL*
Salmonella species	*Streptococcus pneumoniae*	*CTX-M*
Serratia marcescens	*Streptococcus pyogenes*	Methicillin resistance
Haemophilus influenzae	Yeast	*mecA/C*
Neisseria meningitidis	*Candida albicans*	*mecA/C and MREJ (MRSA)*
P. aeruginosa	*Candida auris*	Vancomycin resistance
Stenotrophomonas maltophilia	*Candida glabrata*	*vanA/B*
	Candida krusei	
	Candida parapsilosis	
	Candida tropicalis	
	Cryptococcus neoformans/Cryptococcus gattii	

MRSA, methicillin-resistant *staphylococcus aureus*; MREJ, mec right extremity junction;

Blood cultures that flagged positive for any ICU patient were immediately notified to the treating physician (typically in the morning hours) and the BCID2 test was authorized at the discretion of the treating physician. The BCID2 report was informed telephonically or accessed on the same day for all samples received. Based on the BCID2 test report, the physician decided on the antibiotic of choice before the end of working hours on the same day, in conjunction with clinical judgment. Final alterations in antibiotic regimen if necessary were made once final DST reports were available.

The usual empiric choice for a community-acquired sepsis at our center was an antipseudomonal carbapenem. Decisions initiated by the clinician based upon the BCID2 were termed as listed in the following:

- **Escalation:** When AMR mechanism was detected, the addition of an antibiotic that is usually expected to cover the genotype of AMR detected [e.g., carbapenem for *CTX-M* gene or polymyxin/ceftazidime-avibactam with or without aztreonam for a carbapenem-resistant (CR) gene].
- **De-escalation:**
  - Replacing broad-spectrum antibiotics with agents of a narrower spectrum or a lower ecological impact on an organism is identified but no AMR gene is detected.
  - Continue/start only carbapenem or switch to the narrower spectrum of coverage.[7]
- **Appropriate empiric choice:** When the empiric antibiotics chosen matched the microbe identified and AMR gene.
- **No action:** Patients with negative BCID2 for both microbe and AMR gene; decision to continue the present antibiotics without any change based on clinical judgment.

Results

The total number of patients studied was 200. Baseline characteristics and findings are depicted in Table 2.

A majority (45.5%) had two blood culture bottles flagged from the same set (one aerobic and one anaerobic blood culture bottle), followed by four bottles (36.5%), three bottles (11.5%), and one aerobic bottle (6.5%). Most bacteremia episodes were monomicrobial (92.5%). Gram stain findings, organism detected, and resistance genes are shown in Tables 3 to 6. Mean run-out time for BCID2 and conventional cultures were 2 hours 49 minutes and 40 hours 21 minutes, respectively. The concordance of bacterial species identification between BCID2 and conventional culture was 99%. The overall survival of patients at discharge was 141 (70.5%).

Concordance between DST and BCID2 expected AMR targets were 97%. Discordance between phenotypic and genotypic DST was observed in six bacterial isolates (3%), all in patients with polymicrobial bacteremia. There was no discordance observed in monomicrobial bacteremia. In 5 patients with discordance, resistance genes were not detected despite phenotypic resistance on DST. It is unclear whether this is due to suboptimal test performance or whether these isolates had resistance mechanisms other than those detected by the test. The additional microbes identified in cultures that were not in targets of BCID2 are depicted in Table 7.

The most common empiric antibiotics given were meropenem (17.5%), meropenem with colistin (17.5%), and ceftazidime-avibactam with aztreonam (12.5%). About 37.5% of the patients had antibiotics de-escalated based on BCID2 results and 17% of the patients' antibiotics were escalated based on BCID2 results. Empiric antimicrobials started during sepsis were considered appropriate in 28% of the patients and continued as directed therapy till the final culture DST was available. Polymyxin-based therapy was

Table 2: Baseline characteristics

Characteristics	*N = 200 (%)*
Mean age (years)	60.38 (Range: 21–98)
Male	125 (62.5%)
Female	75 (37.5%)
Diabetes	119 (59.5%)
Hospitalization above 48 hours at our center or previous hospitalization prior to admission	174 (87%)
Antimicrobial taken for more than 5 days in the last 3 months	149 (74.5%)
Mean NEWS 2 score	11.695
Unstable vital signs based on NEWS 2 score	193 (96.5%)
Prior exposure to cefoperazone–sulbactam (most commonly used antibiotic)	70 (35%)
Prior exposure to carbapenem	65 (32.5%)
Monomicrobial bacteremia	185 (92.5%)
Polymicrobial bacteremia	15 (7.5%)
Number of patients died	59 (29.5%)
Stable condition on discharge	103 (51.5%)
Oxygen support on discharge	38 (19%)
Mean time to BCID2 (hours:minutes)	2:49
Mean time to culture identification and DST (hours: min)	40:21

Table 3: Source of bacteremia

Suspected source of bacteremia as per case records	*N = 200 (%)*
UTI	59 (29.5%)
Central line related	32 (16%)
Ventilator-associated pneumonia	17 (8.5%)
Cholangitis	13 (6.5%)
Pneumonia	12 (6.0%)
SSTI	10 (5.0%)
Spontaneous bacterial peritonitis	10 (5%)
Liver abscess	7 (3.5%)
Necrotizing infected pancreatitis	4 (2%)
Infective endocarditis	2 (1%)
Acute gastroenteritis	2 (1%)
Post-surgical meningitis	1 (0.5%)
Surgical site infection	1 (0.5%)
Septic arthritis	1 (0.5%)
Perforative peritonitis	1 (0.5%)
Other intra-abdominal infection	1 (0.5%)
Unclear	27 (13.5%)

SSTI, skin and soft tissue infection; UTI, urinary tract infection

Table 4: Smear findings

Smear findings	*N = 200 (%)*
Gram-negative bacilli	176 (88%)
Gram-positive cocci	12 (6%)
Gram-positive yeast	3 (1.5%)
GNB + GPC	5 (2.5%)
GNB + GPY	1 (0.5%)
GNB + GPB	1 (0.5%)
GPC + GPY	2 (1%)

GNB, gram-negative bacilli; GPB, gram-positive bacilli; GPC, gram-positive cocci; GPY, gram-positive yeast

Table 5: Organism detected in BCID2

Organisms detected in BCID2 in patients with monomicrobial bacteremia	*(N = 185)*
E. coli	55 (27.05%)
K. pneumoniae	47 (23.5%)
P. aeruginosa	15 (7.5%)
A. baumannii	13 (6.05%)
Staphylococcus species	6 (3%)
Salmonella species	5 (2.5%)
E. cloacae	3 (1.5%)
S. marcescens	2 (1.0%)
S. aureus	2 (1.0%)
Proteus species	2 (1.0%)
C. auris	2 (1.0%)
Pneumococcus	1 (0.5%)
Staphylococcus epidermis	1 (0.5%)
No organism identified	31 (15.5%)

Table 6: The AMR targets identified in BCID2

AMR targets detected	*N = 200 (%)*
Gram-positive targets	
Mec A/C	10 (5.00%)
Mec A/C and MREJ	2 (1.0%)
Gram-negative targets	
CTX-M	38 (19.00%)
NDM	9 (4.5%)
Mixed targets	
CTX-M, OXA-48-like	19 (9.5%)
CTX-M, NDM, OXA-48-like	15 (7.5%)
CTX-M, NDM	10 (5.0%)
CTX-M, MecA/C	1 (0.5%)
CTX-M, NDM, OXA-48-like, VANA/B	1 (0.5%)
No targets identified	95 (47.5%)

discontinued after a single empiric dose in 138 patients (69%) based on BCID2 reports. Antimicrobials on 35 patients (17.5%) were not based on BCID2 as there were no appropriate bacteria, AMR targets detected and empiric antibiotics started which was continued till the final DST was available.

Table 7: Additional organisms identified in culture not found in BCID2 targets

Organisms detected in blood cultures but not on the BCID2 panel	*N = 40 (%)*
Burkholderia pseudomallei	8 (4%)
Burkholderia cenocepacia	5 (2.5%)
Ralstonia pickettii	3 (1.5%)
Elizabethkingia anophelis	3 (1.5%)
Aeromonas hydrophila	2 (1.0%)
Salmonella paratyphi A	2 (1.0%)
Achromobacter xylosoxidans	1 (0.5%)
Aeromonas jandaei	1 (0.5%)
Bacillus cereus	1 (0.5%)
Chryseobacterium indologenes	1 (0.5%)
Enterococcus avium	1 (0.5%)
Kluyvera cryocrescens	1 (0.5%)
Leuconostoc pseudomesenteroides	1 (0.5%)
Morganella morganii	1 (0.5%)
Parabacteroides distasonis	1 (0.5%)
Pasteurella multocida	1 (0.5%)
Providencia rettgeri	1 (0.5%)
Pseudomonas putida	1 (0.5%)
Staphylococcal hominis	1 (0.5%)
Saprochaete capitata	1 (0.5%)
Trichosporon asahii	1 (0.5%)
Trichosporon inkin	1 (0.5%)
P. aeruginosa	1 (0.5%)

Discussion

Conventional culture methods for the identification of microbes from blood cultures take 48–72 hours to give final results. The FilmArray blood culture ID (FA BCID) uses multiplex PCR analysis and includes 27 targets (11 gram-negative and 8 gram-positive bacteria, 5 *Candida* spp., and 3 antibiotic resistance markers) directly from positive blood culture bottles in 1 hour.[7] However, this earlier version lacked probes for CTXM-1 and important carbapenemase genes (e.g., OXA-48-like) and was of limited utility in gram-negative bacteremias although it was useful in the management of gram-positive bacteremias in a prior analysis from our center.[4]

Our results highlight the clinical significance of utilizing the BCID2 panel in treating critically ill patients with sepsis. Our patients had a mean NEWS 2 score of 11.695, developed bacteremia after several days of hospitalization in our center or elsewhere, and had been exposed to antimicrobials, making information on early organism identification and resistance pattern very valuable as depicted in Table 2. In our study, the mean run-out time for BCID2 and conventional cultures were 2 hours 49 minutes and 40 hours 21 minutes, respectively, resulting in same-day availability of organism ID and resistance data, as opposed to 1–2 days later. In a study by Arjun et al.,[5] the median time from blood culture flag to identification and susceptibility result by the conventional method was 43.3 hours and the lead time to result by BCID2 panel (difference in time between BCID2 and conventional method) was 25.25 hours.

In our study, the majority (88%) of BCID2 requests from the ICU were for gram-negative bacteria as depicted in Table 4, perhaps reflecting the greater concern in clinicians' minds regarding resistance in gram-negatives as opposed to gram-positive bacteria.[8–10] The predominant microbes in our study of monomicrobial bacteremia were dominated by *Escherichia coli* (27.5%), followed by *Klebsiella pneumoniae* (23.5%), *Pseudomonas aeruginosa* (7%), and *Acinetobacter baumanii* (6.5%). The commonest sources of bacteremia in our study were urosepsis (29.5%) and central line related (16%), followed by VAP (8%) and unclear focus (13.5%).

We found 99% concordance between BCID2 and cultures in the identification of microbes. BCID2 missed the identification of only one *Pseudomonas* in a patient with polymicrobial bacteremia. The other 40 missed microbes were not listed on the BCID2 panel and were picked up in culture as depicted in Table 7. Future versions of the test may need to include additional targets for nonfermenting gram-negative bacilli such as *Burkholderia* spp, *Ralstonia*, and *Elizabethkingia—all* of which were encountered in our study. In a prospective study from India by Shah et al.[9] A total of 38 microorganisms were identified from 30 patients. In 70% (21/30) of patients, the result of BCID2 and microbial culture matched completely, in 23% (7/30) they matched partially, and in 6% they did not match. The match between genotypic assay and phenotypic susceptibility was 100%. Shah et al.[11] found that BCID2 results led clinicians to modify prescribed antimicrobials in 33% of cases, with 23.3% of patients experiencing escalation and 10% experiencing de-escalation. A comparative study by Peri et al. found that out of 60 monomicrobial blood cultures, BCID2 correctly identified 55 out of 56 (91.7%) on-panel pathogens, demonstrating an overall concordance of 98%. In 4 out of 60 cases, BCID2 did not detect any target and these all grew BCID2 off-panel bacteria.[12]

Peri et al. emphasized that concordance between conventional testing and BCID2 for polymicrobial blood cultures is lower than that for monomicrobial blood cultures observed in their study. In a study by Berinson et al. BCID2, results were concordant with the standard of care (SOC) in 159/180 (88.3%) blood cultures; 68/74 (91.9%) and 71/74 (96.0%) of all samples growing monomicrobial, gram-positive or gram-negative pathogens, respectively.[13] Discordance was seen in four patients, which were polymicrobial bacteremia.

Regarding the AMR genes detected, CTX-M was detected in 38 patients (19%), and CR genes were detected in 54 patients (27%). Carbapenem resistance (CR) was common in previous studies from our center.[8,9] Distribution of CR genes was equal between NDM and OXA-48-like (13.5% each). A study on the XpertCarba–R molecular test done on bacteremia by Rajendran et al.[14] observed that the distribution of CR genes overall was OXA-48-like (29/58, 50%), followed by NDM (19/58, 32.7%), followed by OXA-48 and NDM coexpression (9/58, 15.51%).

Using alternatives to polymyxin for carbapenemase-producing *Enterobacterales* such as ceftazidime–avibactam monotherapy (for KPC and OXA-48) and in combination with aztreonam (for NDM-1) based on positive synergy testing is key to discontinuing polymyxins.[15,16] This is however critically dependent on the exact enzyme produced by the organism and carries important implications for individual patient outcome and antimicrobial stewardship.[17,18] We do not recommend using CR gene detection to predict response in nonfermenters such as *Pseudomonas* and *Acinetobacter* as these can be CR through other mechanisms (porin channels or efflux pumps) in addition to the expression of carbapenemases. This is also a limitation of tests such as XpertCarba–R which detect resistance genes but do not give organism identification.[17–19]

Although we found that the earlier version of BCID is useful in gram-positive bacteremia in our previous study,[4] less than 10% of our patients had the test ordered for this indication in the current study as clinicians largely considered the test most useful for identifying and detecting resistance among gram-negative bacteremia.[8]

One of the major observations in our study was that overall, BCID2 played a key role in tailoring antimicrobials in 82.5% of the patients in our study. Escalation of antibiotics in 37% and de-escalation in 17% of the patients was based on BCID2 reports. About 28% of the patients continued with their empiric antimicrobials as it was deemed appropriate based on the BCID2 report. Starting coverage or stopping inappropriate for extended spectrum beta lactamases (ESBL) producers in community-acquired gram-negative bacteremia and CR coverage in hospital-acquired bacteremia was greatly facilitated. Another key finding in our study was noting the reduction of polymyxin therapy based on BCID2. Polymyxin-based therapy was stopped after an initial dose in 138 patients (69%) based on BCID2, reducing both the risk of nephrotoxicity and observed poor outcomes with this drug.[10]

Limitations

The test was ordered at the discretion of the treating physician and was ordered mostly for gram-negative bacteremia. Whole genome sequencing to identify missed genes was not done for the isolates. The test was done only during working hours and was not done around the clock. This study was not a prospective study and did not have a control arm of patients with bacteremia who were managed without BCID2.

Conclusion

In critically ill patients with bacteremia, BCID2 rapidly identifies microbes and AMR genes and is much faster than conventional culture and sensitivity testing. Our findings support the use of the BioFire FilmArray BCID2 panel as an adjunct to conventional culture methods, especially in critically ill patients with hospital-acquired bacteremia and prior antibiotic exposure. This panel provides rapid results which will guide appropriate same-day management of empirical antimicrobial therapy in a large proportion of patients with bacteremia. In terms of antimicrobial stewardship, it assists both in an escalation of antibiotics if patients are not already on CR/ESBL cover, as well as de-escalating therapy if already initiated before receiving results of DST. In the era of newer drugs active against carbapenemases such as ceftazidime-avibactam, it helps to decide early appropriate polymyxin-sparing therapy based on the exact mechanism of resistance. We recommend that all ICU which encounter a high rate of CR/ESBL organisms routinely incorporate the test in their antibiotic decision-making process.

Authors' Contributions

VKV: Contributed to design, conceptualization, data collection, analysis, interpretation, and preparation of the first draft.

PSN, GR, and VR: Contributed to design, conceptualization, review of the data collected, review of the analysis, and interpretation. Involved in revising the draft critically.

SN and CC: Contributed technical support in their respective fields of microbiology and molecular biology. Assisted in data

collection, interpretation, and analysis of the data and reviewed the draft critically for revisions.

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