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Original Research Article

Clinical utility of the FilmArray blood culture identification 2 panel in identification of microorganisms and resistance markers from positive blood culture bottles

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ABSTRACT

Bloodstream infections (BSIs) remain a leading cause of morbidity and mortality especially in intensive care units across the world and timely appropriate antimicrobial therapy is a corner stone in its treatment

Aim: (i) To compare the time difference to diagnose BSIs between FABCID2 and identification and sensitivity by automated systems (ii) To analyse the clinical utility of the FABCID2 panel in positive blood samples among ICU patients.

Materials and Methods: This was a prospective study done from July 2020 to August 2020 where consecutive thirty positive blood culture received from ICUs were processed for gram stain, culture and antimicrobial susceptibility along with performing PCR with BioFire FilmArray Blood Culture Identification2 (FABCID2) Panel. Time line of positive blood culture from receipt to report generation at multiple points were captured along with impact of results in terms of changing antimicrobial therapy of the patients and outcome.

Results: A total of 38 microorganisms were identified from 30 patients. In 70% (21/30) of patients, the result of FABCID2 and growth in culture matched completely, in 23% (7/30) they matched partially and in 6% they did not match. The match between genotypic markers in the assay and phenotypic susceptibility was 100%. FABCID 2 results prompted clinicians to change the antimicrobials prescribed to 33% of total patients (escalation was done in 23.3% of patients and de-escalation was done in 10%.

Conclusion: Clinical utility of the FABCID2 Panel in Identification of microorganisms and resistance markers from Positive Blood Culture Bottles is significant which should be used in conjunction with conventional methods to impact patient outcome and antimicrobial stewardship program.

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1. Introduction

Bloodstream infections (BSIs) remain a leading cause of morbidity and mortality especially in intensive care units across the world and timely appropriate

antimicrobial therapy is a corner stone in its treatment.¹ Current microbiological methods for identification and susceptibility of microorganisms from blood cultures, take a considerable time, from one to three days. Several microbiological methods for rapid and specific identification of infectious agents from positive blood

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culture bottles have been suggested, including PCR coupled to high-resolution melting curve analysis as the FilmArray Blood Culture Identification Panel 2 (FABCID2). This is an easy to perform technology for identification of microorganism and resistant gene markers from positive blood culture bottles of patient.

The aims of the present study were (i) To compare the time difference to diagnose BSIs between FABCID2 and identification and sensitivity by automated systems (ii) To analyse the clinical utility of the FABCID2 panel in positive blood samples among ICU patients.

2. Material and Methods

This was a prospective study done from July 2020 to August 2020 where consecutive thirty positive blood culture received from ICUs were processed for gram stain, culture and antimicrobial susceptibility along with performing PCR with BioFire FilmArray Blood Culture Identification 2 (FABCID2) Panel (BioMérieux Ltd, France). The blood culture were processed by Bactec, BD, USA which is an automated continuous monitoring system. Gram stains and subculture on 5% sheep blood agar and MacConkey's agar (BioMérieux Ltd, France) was done for all positive blood culture bottles. The microorganisms grown on the agar plates were identified by VitekMS (BioMérieux Ltd, France) and susceptibility was performed using by Vitek2 (BioMérieux Ltd, France). Identification of positive blood culture broth was not done using VitekMS (MALDI-ToF). FABCID2 is a multiplexed nucleic acid amplification which is used for the simultaneous qualitative detection and identification of multiple bacterial and yeast nucleic acids and select genetic determinants associated with antimicrobial resistance which are listed in Table 1.² It detects 43 targets. It detects the genetic resistant markers for various antimicrobials like carbapenem, vancomycin, methicillin and colistin. Negative results for these select antimicrobial resistance gene and marker assays do not indicate susceptibility, as multiple mechanisms of resistance to these antimicrobials exist.³ Quality control for all the reagents and methodology were adopted as per national accreditation guidelines.⁴

All positive blood culture bottles were processed in accordance with manufacturer instructions.² The relevant well of the FABCID2 pouch was loaded with the provided hydration solution followed by 200 μ L of broth from a positive blood culture bottle, followed by the addition of the provided sample buffer into the sample injection well. The pouch then was loaded into the BioFire FilmArray instrument. Thereafter, automated processing took place within the instrument, involving nucleic acid purification, multiplex PCR and lastly analysis of DNA melting curves to confirm and identify the presence of bacterial and fungal targets as well as antimicrobial resistance genes within the culture being tested. Correlation of genotype of resistance

markers and phenotypic sensitivity was done.

Paired blood culture were sent from ICU when patients were suspected to have sepsis. One FABCID2 panel was used for first positive culture of the patient. Patients' demographic details were captured. Results of FABCID2 Panel as and when available were informed to the intensivists by sending photographic image using the phone. Result of identification of microorganism and antimicrobial susceptibility too were informed to intensivists as soon as they were available. Time line of positive blood culture from receipt to report generation at multiple points were captured along with impact of results in terms of changing antimicrobial therapy of the patients and outcome.

3. Results

A total of thirty patient's consecutive positive blood culture from mixed intensive care units were processed. There were 1 neonate, 2 paediatric patients and 27 adult patients included in the study group. These were all clinically relevant cultures and they were neither colonisers nor commensals. However, they included both community acquired infections and hospital acquired infections. Blood was collected from peripheral blood vessel among 50% arterial line (16.7%), central Line (30%) and Haemodialysis catheter (3.3%) of the patients. The comorbidity among the patients included Covid infection,⁵ renal disease,⁴ neurological disease,⁶ vascular disease,² Malignancy,³ end stage liver disease.¹

A total of 38 microorganisms were identified from 30 patients. 23 patients had single microorganism identified and 7 patients had more than one microorganisms causing infection. There were 82% gram negative bacilli, 11% gram positive cocci and 8% yeast. Of 31 GNB, 61% were enterobacterales. The spectrum of microorganisms grown among these patients is mentioned in Figure 1. In 70% (21/30) of patients, the result of FABCID2 and growth in culture matched completely, in 23% (7/30) they matched partially and in 6% they did not match as seen in Table 2. Statistical parameters are calculated considering culture as gold standard in Table 3. In FABCID2 panel, there were genetic resistance marker detected; blaNDM,² blaOXA 48² and blaCTX-M.⁷ There was no blaKPC detected. Mean and median time for blood culture bottles to flag positive, providing identification antimicrobial susceptibility results and FABCID2 reports as mentioned in Table 4. Yeast took longer time in both growth and Susceptibility testing. It took additional 21 hours on an average to give identification after the blood culture bottle flagged positive and appx. 28 additional hours to give antimicrobial susceptibility after FABCID2 reports were available as mentioned in Table 5. The match between genotypic markers in the assay and phenotypic susceptibility was 100%. FABCID 2 results prompted clinicians to change the antimicrobials prescribed to 33% of total patients (escalation was done in 23.3% of

patients and de-escalation was done in 10%). Four patients (14.8%) were critically ill, and they passed away before the blood culture results were provided. The others were eventually discharged from the hospital.

4. Discussion

Tertiary care hospital ICUs have a high burden of multi drug resistant microorganisms in India posing therapeutic challenges. Identification and susceptibility testing of microorganisms growing in blood culture in shortest turnaround time is one of the key performance indicator for microbiology laboratory which allows adapting and individualising the empirical antimicrobial therapy in patients with blood stream infection by clinician.

The results demonstrates high sensitivity (96.7%) of the FABCID assay which is similar to that reported in previous studies.^{5–8} It is also useful in identifying more than one microorganisms causing infection which may be missed if one microorganism over grows another one in blood culture bottle.

There was partial match in 20% (6/30) patients with multi-microbial infection and discrepancy in another 10% of the patient's results. A few discrepancy are due to absence of target like in *Elizabethkingae* sp. The other can be due to variation in load of detection by the system. Overall, the results were accurate and reproducible as seen other studies.^{5–8}

The crucial advantage of this assay is microorganism identification within 1.5 hours of positive blood cultures. The time saved was approximately 21 hours for identification to 28 hours for susceptibility. O Altun et al. has reported similar saving of time.⁹ In our study, results of FABCID2 prompted change in antimicrobial therapy in 33% patients in ICU. That means appropriate therapy could be given to these patients almost a day earlier. Similar change in therapy is demonstrated by Roxanne Rule et al.⁶ MALDI-TOF MS can be utilised for direct identification on flagged positive blood culture or after growth on solid media to decrease time to identify the pathogen. We performed identification from the colonies. The global agreement of the FABCID2 with the reference technique was 91.5% significantly higher than that with the fast MALDIToFMS assay (79.7%), $P < 0.01$) as demonstrated by Paul V et al.⁵ and by combining the two approaches, 93.5% of the bottles were identified correctly at day 0 by them. Also, detection of resistance in MALDIToF is an upcoming phenomenon as yet.

There are other commercial PCR technology that allows detection of resistance marker without identification of organisms like Carbapenemase detection or *mecA*, Van A/B detection. However, absence of these genes without identification of bacteria might restrict its use in clinical settings as there may be presence of other mechanisms in pathogen like *Pseudomonas* sp. might also be conferring

resistance to it.³

There has been also increase in numbers of patients with polymicrobial BSIs, possibly due to the advances in medicine that allow survival of patients helped by various external and internal invasive medical support despite very low immunity. Therefore, the ability to identify several different isolates is an important parameter especially in ICUs. The use of rapid identification methods, including direct MALDI-TOF, in identification of microorganisms in samples with polymicrobial growth is quite low.¹⁰

Accurate diagnosis and early treatment certainly will contribute in decreasing patient's length of stay, cost of therapy and improving outcome. Antimicrobial therapy was deescalated in 10% of the patients and thus system has an important role in decreasing antimicrobial pressure in the unit and Antimicrobial Stewardship Program of the hospital.

Strategizing and optimising the use of FABCID2 can depend upon the type of the unit. High investment, running cost and limited targets (customised by manufacturer), the FABCID2 could be dedicated for critical or high risk patients who need an expeditious alteration of their antimicrobial treatment. Fiori et al. have suggested,¹¹ to reserve the approach to those bottles that failed identification by the fast MALDIToFMS method. The study of Pardo et al.¹² and K Vaerdakas et al.¹³ have demonstrated cost effectivity of the FABCID2 assay, when coupled with antimicrobial stewardship intervention, to improve patient care. In another meta-analysis that included 31 studies and 5920 patients, Timbrook et al.¹⁴ showed that molecular rapid diagnostic tests in bloodstream infections were associated with significant decrease in mortality risk if associated with an antimicrobial stewardship program.

Pathogen-specific real-time PCR,¹⁵ fluorescence in situ hybridization using peptide nucleic acid probes (PNA-FISH),¹⁶ nanosphere technology¹⁷ etc. have been also described for rapid identification of microorganisms from positive blood culture bottles. However, the tests yet are labour intensive and not comprehensive. Also, they cannot determine resistant markers, including carbapenemases.

The newer high-technology diagnostics technologies need to be adopted alongside conventional methods; rationalising and strategizing cost effectivity; to find ways to integrate rapid diagnostics into clinical care and link results to treatment and better outcomes. Newer local cost effective technologies need to be developed for Indian patients which cover Indian epidemiology.

There are some shortfalls in this study that mainly includes small number of patients and correlation of result with sequencing technology. A few particular microorganisms, like *Serratia* spp. and *Salmonella* spp., was not part of study.

Table 1: Microorganisms and resistance markers detected by FABCID2 panel

Gram Negative Bacilli	Gram Positive Cocci	Yeast	Resistance Marker
Acinetobacter	Enterococcus faecalis	Candida albicans	NDM IMP VIM KPC
calcoaceticus-baumannii complex	Enterococcus faecium		CTX-M and OXA-48-like
Enterobacterales Enterobacter cloacae complex	Staphylococcus spp.	Candida krusei	mcr-1
Escherichia coli	Staphylococcus aureus		
Klebsiella aerogenes	Staphylococcus epidermidis		
Klebsiella pneumoniae oxytoca	Staphylococcus lugdunensis		
group Proteus spp. Salmonella spp. Serratia marcescens			
Pseudomonas aeruginosa	Streptococcus spp.	Candida auris	mecA/C MREJ(MRSA)
	Streptococcus agalactiae (Group B)		
	Streptococcus pneumoniae		
	Streptococcus pyogenes (Group A)		
Stenotrophomonas maltophilia	Listeria monocytogenes	Candida parapsilosis	vanA/B
Haemophilus influenzae		Candida glabrata	
Neisseria meningitidis (encapsulated)		Candida tropicalis	
Bacteroides fragilis		Cryptococcus neoformans/gattii	

Table 2: Difference between blood culture and FABCID2 results

Difference	Number
Patient cultures grew additional bacteria than what FABCID2 identified	4
patients culture did not grow all bacteria as identified by PCR panel	2
Patient culture the PCR panel identified as Pseudomonas aeruginosa but the culture grew Burkholderia cepacia.	1
Acinetobacter grew in culture but was not identified on PCR panel	1
PCR panel could not identify any organism as Elizabethkingae as it is not part of the target. In one case	1

Table 3: Statistics of the test considering culture results as gold standard

	Value	95% CI
Sensitivity	96.77%	83.30% to 99.92%
Specificity	85.71%	42.13% to 99.64%
Positive Likelihood Ratio	6.77	1.10 to 41.63
Negative Likelihood Ratio	0.04	0.01 to 0.26
Positive Predictive Value (*)	96.77%	83.00% to 99.46%
Negative Predictive Value (*)	85.71%	46.01% to 97.69%

Table 4: Turn around time of blood culture report and PCR panel report

	Time to flag positive	Time to identification	Time to sensitivity	Time to Give PCR panel Report
Mean time in hours	23.4	43.9	59	26.3
Median Time in hours	19	42	49	21

Table 5: Change of antimicrobials done depending upon FABCID2 panel report

Escalation to Colistin	1
Escalation to Minocycline	1
Escalation to CeftazidimeAvibactam	1
Escalation to Teicoplanin	2
Escalated to Anidulafungin	1
Escalation to Teicoplanin	1
Deescalation of Meropenem and Colistin	1
Deescalation of Colistin	1
Deescalation of Tigecycline and PolymyxinB	1
Total	10 (37%)

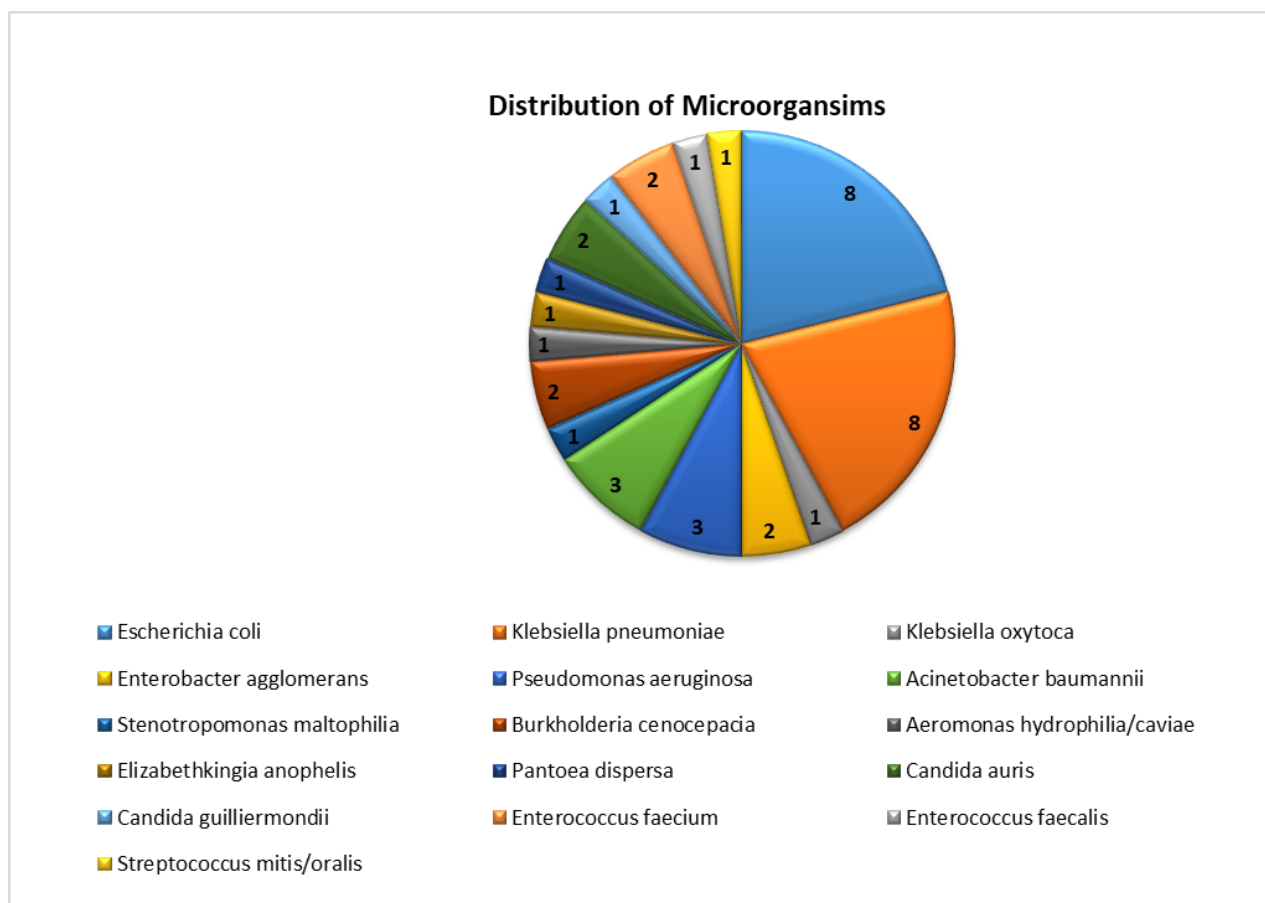


Fig. 1: Distribution of microorganisms in blood culture

5. Conclusion

Clinical Utility of the FABCID2 panel in identification of microorganisms and resistance markers from positive blood culture bottles is significant and can be optimised for some units in conjunction with conventional methods to impact patient outcome. Additionally, it contributes in the prevention of emergence and transmission of antimicrobial resistance.

6. Conflicts of Interest

The authors declare no conflicts of interest.

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