Rapid Detection of Bloodstream Pathogens in Liver Transplantation Patients With FilmArray Multiplex Polymerase Chain Reaction Assays: Comparison With Conventional Methods

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ABSTRACT

Background. Bloodstream infection (BSI) is an important concern in transplant patients. Early intervention with appropriate antimicrobial therapy is critical to better clinical outcome; however, there is significant delay when conventional identification methods are used.

Methods. We aimed to determine the diagnostic performance of the FilmArray Blood Culture Identification Panel, a recently approved multiplex polymerase chain reaction assay detecting 24 BSI pathogens and 3 resistance genes, in comparison with the performances of conventional identification methods in liver transplant (LT) patients. A total of 52 defined sepsis episodes (signal-positive by blood culture systems) from 45 LT patients were prospectively studied.

Results. The FilmArray successfully identified 37 of 39 (94.8%) bacterial and 3 of 3 (100%) yeast pathogens in a total of 42 samples with microbial growth, failing to detect only 2 of 39 (5.1%) bacterial pathogens that were not covered by the test panel. The FilmArray could also detect additional pathogens in 3 samples that had been reported as having monomicrobial growth, and it could detect *Acinetobacter baumannii* in 2 samples suspected of skin flora contamination. The remaining 8 blood cultures showing a positive signal but yielding no growth were also negative by this assay. Results of *MecA*, *KPC,* and *VanA/B* gene detection were in high accordance. The FilmArray produced results with significantly shorter turnaround times (1.33 versus 36.2, 23.6, and 19.5 h; $P < .05$) than standard identification methods, Vitek II, and Vitek MS, respectively.

Conclusions. This study showed that the FilmArray appeared as a reliable alternative diagnostic method with the potential to mitigate problems with protracted diagnosis of the BSI pathogens in LT patients.

BLOODSTREAM INFECTION (BSI) is one of the major complications in patients with liver transplantation (LT). Approximately 28% to 80% of these patients have at least one clinically important episode of BSI during the first year of the transplantation, and most of them occur in the first month after the procedure [1,2]. BSI is an independent risk factor for mortality in LT patients associated with almost a 4- to 9-fold higher risk of death and poorer survival rates compared with LT patients without BSI [3,4]. Additionally, BSI is a significant cause of morbidity because of longer hospitalization, multi-organ dysfunction, and graft rejection [5–7].

Blood culture is the gold standard for detection of BSI pathogens. When microbial growth is detected in a culture bottle, at least an additional 24 h are required to identify the infecting agent. In some situations such as multimicrobial

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Table 1. Microorganisms Detectable by Use of the FilmArray Test

Gram-Negative Bacteria	Gram-Positive Bacteria	Yeast	Antimicrobial Resistance Genes
Enterobacteriaceae	*Staphylococcus spp*	*Candida albicans*	*mecA*: Methicillin resistance gene
Escherichia coli	*Staphylococcus aureus*	*Candida glabrata*	*vanA/B*: Vancomycin resistance gene
Enterobacter cloacae complex	*Streptococcus spp*	*Candida krusei*	KPC: Carbapenem resistance gene
Klebsiella oxytoca	*Streptococcus agalactiae*	*Candida parapsilosis*	
Klebsiella pneumoniae	*Streptococcus pyogenes*	*Candida tropicalis*	
Serratia marcescens	*Streptococcus pneumoniae*		
Proteus spp	*Enterococcus spp*		
Acinetobacter baumannii	*Listeria monocytogenes*		
Haemophilus influenzae			
Neisseria meningitidis			
Pseudomonas aeruginosa			

growth, the time needed may be longer, and it may take 48 to 72 h before results are available. On the other hand, time is a critical factor for LT patients, particularly in the early postoperative period because receiving inappropriate empiric antimicrobial therapy is directly related to deteriorated clinical outcomes [8]. Nevertheless, treatment delay for targeted antimicrobial(s) frequently occurs because of a number of time-consuming microbiological procedures, including conventional identification methods.

The FilmArray Blood Culture Identification Panel (BCID) received Conformite Europeenne (CE) - In Vitro Diagnostics (IVD) approval in 2013 in Europe for use in in vitro diagnostic examinations. It is a qualitative, multiplexed, nucleic acid–based, in vitro diagnostic assay designed to rapidly identify (1 to 2 h) the 24 most common BSI pathogens in blood cultures, including 10 Gram-negative and 9 Gram-positive bacteria and 5 yeasts (Table 1). The panel also contains assays for detection of 3 clinically important genetic determinants of antimicrobial resistance, *MecA*, *VanA/B*, and *KPC*. Although limited data are available, the clinical performance of the FilmArray in terms of validity, reliability, reproducibility, and turnaround time is promising [9,10]. Therefore, it might have potential for early diagnosis of sepsis pathogens in LT patients. To date, the FilmArray has been studied in a limited number of adult and pediatric patient populations, and there is still no study on its clinical relevance in patients with organ transplantation. In the present study, we aimed to compare the diagnostic performance of the FilmArray in LT patients with sepsis with conventional microbiological methods.

MATERIALS AND METHODS

Patients and Study Design

This prospective study was conducted between March and December 2013 as a collaboration between the general surgery, infectious diseases, and microbiology departments at the Liver Transplantation Institute of Turgut Ozal Medical Center. A total 45 LT patients diagnosed with postoperative sepsis were included. The diagnosis of sepsis was established by general surgeons and infectious disease specialists, according to the criteria of Surviving Sepsis Guidelines [11]. Blood samples were aseptically collected, inoculated into BactAlert (Bio Mérieux, France) blood culture bottles, and incubated in a BacT/ALERT 3D automated blood culture instrument (Bio Mérieux, France) for 7 days. One set of blood culture bottles (2 bottles from 2 different body areas) was obtained for each episode. If a positive signal emerged, indicating microbial growth in the bottle, 2 aliquot fluid samples were aspirated from the bottle, and 1 was subjected to conventional culture and identification procedures and the other was subjected to molecular analyses (for FilmArray assay).

Conventional culture and identification methods included 2 steps. At the first step, 1 of the obtained aliquots from a positive culture bottle was subcultured on agar plates such as sheep blood agar, eosin methylene blue agar, chocolate agar, and Sabouraud dextrose agar (Oxford, United Kingdom). After incubation, the plates were evaluated by a medical microbiologist. If required, the plates were subcultured to purify the organisms (in cases of multi-microbial growth). At the second step, 2 investigators (blind to each other) carried out different procedures. One investigator identified the pathogens through the use of classic microbiological methods, and the other investigator identified the pathogens grown on the agar plates through the use of Vitek II and Vitek MS systems. A different microbiologist carried out the identification process with the use of the FilmArray from the second aliquot fluid obtained from the positive bottle.

All the investigators recorded the time taken throughout the laboratory procedures until the results were available.

Conventional Identification Methods

We selected 3 commonly used conventional methodologies for identification of the pathogens that were isolated from the positive blood culture bottles, including classic microbiological tests, Vitek II and Vitek MS. Gram staining was performed directly on each positive sample. Classic microbiological procedures included a number of analyses described in the *Clinical Microbiology Procedures Handbook* [12]; these included colony morphology, Gram staining, movement, catalase, oxidase, and coagulase tests and biochemical analyses.

The laboratory procedures of the Vitek II system were performed according to the manufacturer's instructions. Briefly, a bacterial suspension was adjusted to a McFarland Standard range, 0.55 to 0.65 for bacteria and 1.8 to 2.2 for yeast in 3 mL of 0.45% sodium chloride solution. This suspension was inoculated to ID cards, ID Gram-positive cocci, ID Gram-negative bacilli, and ID yeast. Next, the inoculated cards were placed into the Vitek II reader incubator module. The cards were automatically read every 15 min, and the results were automatically generated by the system.

The laboratory procedures of the Vitek MS system were performed according to the manufacturer's instructions. Briefly, cells from representative single bacterial colonies grown on an agar plate were directly smeared onto a target spot of a steel target plate, overlaid with 1 μL of matrix, and air-dried within minutes at room

temperature. Definition of each smeared colony on spot took 2 min by VITEK MS (bioMérieux, France). Mass spectra were generated with the use of the VITEK MS software program for automatic measurement and identification. The score values were determined by comparison against the super-spectra for confidence identification, and they allowed the identification at the family, genus, and species levels.

FilmArray Multiplex Analysis Directly on Positive Blood Cultures

Samples from positive blood cultures were loaded into the testing cartridge for molecular analysis. After hydrating the pouch with 1.0 mL of hydration solution, 300 μL of blood sample from positive blood culture bottles was diluted in 0.5 mL of sample buffer, of which 300 μL was injected into the sample pouch, which was then loaded onto the instrument. After entering the sample identification, the instrument was started. The testing pouch contained all the reagents for nucleic acid extraction, first-step multiplex Blood Culture Identification Panel polymerase chain reaction (PCR) amplification, and second-step real-time PCR amplification with one single specific primer pair. For each microbial agent, the second-step PCR was performed in triplicate. The software automatically analyzed the melting curve of the second-step PCR to report the results as positive or negative for a certain microorganism present in the test spectrum.

Resistance Screening

The antimicrobial resistance determinants included in the FilmArray assay were evaluated by means of conventional and molecular methods. Methicillin resistance for staphylococci was evaluated with the use of 2 methods, including the cefoxitin disk method according to Clinical and Laboratory Standards Institute (CLSI) criteria [13] and a PCR assay for detection of the *MecA* gene according to previously described protocol [14]. Vancomycin resistance for enterococci was evaluated by means of the vancomycin disc diffusion method according to CLSI criteria and a previously described PCR method [15]. *Klebsiella pneumonia* carbapenemase (*KPC*) gene, encoding carbapenem resistance among Gram-negative bacilli, was evaluated with the use of a PCR method described by Monteiro et al [16].

Data Collection and Analysis

Demographic and clinical data from the LT patients were prospectively collected. The duration of each laboratory process was recorded. For the conventional methods, the time was measured from the point when the subculture was performed on solid agar medium from the positive bottle to the point when the results were available. For the FilmArray assay, the time was measured from the point when the molecular study was started to the point when the results were available. The total time scores for each method were expressed as mean number of hours.

The classic microbiological identification methods were accepted as the gold standard [17,18]. The parameters of the diagnostic performance for identification methods included sensitivity, specificity, and the required time span for the results to become available. Quantitative data were statistically compared by use of the χ^2 test, and a value of $P < .05$ was considered statistically significant.

RESULTS

Patients and BSI Pathogens

A total of 202 patients underwent LT in the study period, and 58 LT patients were diagnosed with sepsis. Thirteen patients were excluded from the study because the FilmArray was not studied for these patients. Among these, 52 signal-positive BSI samples belonging to 45 patients were studied. The mean age of the patients was 46 years (range, 21 to 64 years), and sex distribution was 29 of 16 (M/F). Demographic and clinical characteristics of the study population are presented in Table 2.

Table 2. Demographics and Clinical Properties of the Liver Transplant Patients Studied

	n = 45
Age	46.1 (21–64)
Sex	
Male	29
Female	16
Donors	
Live	39
Cadaveric	6
Main reason leading to liver transplant	
Cryptogenic cirrhosis	17
Hepatitis A	1
Hepatitis B	13
Hepatitis B + D	4
Hepatitis C	4
Hepatocellular carcinoma	3
Caroli disease	1
Budd-Chiari	1
Wilson disease	1

Forty-four of the total 52 (84.6%) samples exhibited microbial growth. In the remaining 8 samples, both Gram staining and culture were negative, despite bottles yielding a positive signal in the blood culture device. Gram-negative bacteria were identified in 27 samples, including 8 samples with *Escherichia coli*, 7 with *K pneumoniae*, 5 with *Acinetobacter baumannii*, 3 with *Enterobacter cloacae*, 2 with *Morganella morganii*, and 2 with *Pseudomonas aeruginosa*. Gram-positive bacteria were identified in 12 samples including 6 with *Staphylococcus aureus*, 2 with *Enterococcus faecium*, 2 with *Streptococcus spp*, and 2 with coagulase-negative staphylococci (CoNS). In 2 of 3 samples, *Candida albicans,* and, in the remaining sample, non-albicans *Candida* spp was identified. There was no discordance between the results of the classic identification methods and identification by means of Vitek II and Vitek MS.

Polymicrobial growth was detected in 2 samples and included *Staphylococcus* spp and *Streptococcus* spp. The clinical microbiologist interpreted the results from these 2 samples as skin contamination; hence, the Vitek II and Vitek MS results were not studied for these 2 samples.

Direct Gram staining of positive samples yielded 22 Gram-negative bacilli and 17 Gram-positive cocci.

Performance of FilmArray Assay

Through the use of classic identification methods, single microorganisms could be identified in all the culture-positive 42 samples. Twelve different species were isolated during the study, and the FilmArray panel covered 11 (91.6%) of these. Compared with the classical identification methods, Vitek II

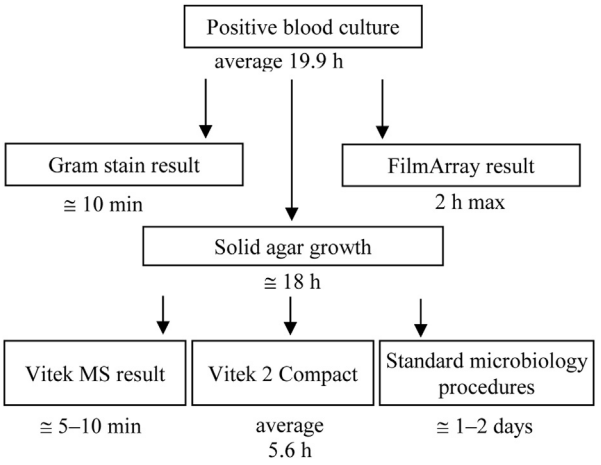

Fig 1. Study diagram and duration of procedures according to each method.

and Vitek MS could identify 42 of 42 (100%) pathogens, and the FilmArray assay could identify 40 of 42 (95.2%) pathogens. The FilmArray failed to identify *Morganella morganii* in 2 samples because this bacterium was not included in the test panel.

The FilmArray assay was negative for 8 samples that gave a positive signal in the blood culture system but yielded no growth in the agar medium.

The sensitivity and specificity of the FilmArray were as follows: for Gram-negatives, 92.5% and 100%, respectively; for Gram-positives, 100% and 100%; and for yeasts, 100% and 100%.

In 3 samples with monomicrobial growth, the FilmArray enabled identification of additional pathogens, including *Enterococcus* spp in 2 samples and CoNS in 1 sample. Furthermore, the FilmArray assay detected 3 different bacteria in each of the 2 samples, which had been reported positive because of contamination by skin bacteria, by the classic identification methods. In addition to *Staphylococcus* spp and *Streptococcus* spp found by the classic method, the FilmArray detected *A baumannii* in these 2 samples. No invalid results were obtained with the FilmArray.

The blood culture method yielded a positive signal within a mean of 19.9 h (SD ± 15.5 h). For the results to become available, the classic identification method took 36.2 h (SD ± 19.2 h), Vitek II took 23.6 h (SD ± 2.23 h), and Vitek MS took 19.5 h (SD ± 15.1 h). The FilmArray assay identified a pathogen in a mean time of 1 h, 20 min (range, 65 to 100 min), and this turnaround time was significantly lesser than that of the conventional methods ($P < .05$). Figure 1 shows the study diagram and the time scores of the included methods.

The FilmArray enabled detection of all four isolates of methicillin-resistant staphylococci (3 methicillin-resistant *S aureus* and 1 CoNS). No enterococci was found positive for the *VanA/B* gene, and all Gram-negative bacteria were negative for *KPC*. Molecular studies confirmed that the isolates found negative for *MecA*, *KPC,* and *VanA/B* genes by FilmArray were also negative.

Table 3 shows the identified pathogens and the sensitivity and specificity scores for each method.

DISCUSSION

LT is the most effective treatment method for patients with end-stage liver failure, and it can save the patient's life. LT requires extremely well-planned and comprehensive pre- and post-operative medical processes, and it comes at a high

Table 3. Identified Pathogens and Resistance Determinants According to Sensitivity and Specificity of Each Method

		FilmArray		Vitek II		Vitek MS	
Microorganism	n	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Gram-negative bacteria	27	92.5	100	100	100	100	100
E coli	8	100	100	100	100	100	100
K pneumoniae	7	100	100	100	100	100	100
A baumannii	5	100	100	100	100	100	100
E cloacae	3	100	100	100	100	100	100
M morgani	2	0	0	100	100	100	100
P aeruginosa	2	100	100	100	100	100	100
Gram-positive bacteria	12	100	100	100	100	100	100
S aureus	6	100	100	100	100	100	100
Enterococcus faecium	2	100	100	100	100	100	100
Streptococcus spp	2	100	100	100	100	100	100
CoNS	2	100	100	100	100	100	100
Fungi	3	100	100	100	100	100	100
C albicans	1	100	100	100	100	100	100
C krusei	2	100	100	100	100	100	100
Antibiotic resistance genes							
Mec A	4	100	100	100	100	–	–
KPC	0	–	100	–	100	–	–
VanA/VanB	0	–	100	–	100	–	–

economic cost. However, despite advances in surgical techniques, post-transplant care, hospital environment, immunosuppression, infectious disease treatment, infection prevention and prophylaxis, and systemic infections are still the leading complications potentially affecting the patient and graft survival [19].

LT patients become more susceptible to microbial agents because of a number of factors, including morbidity because of organ failure at the pre-operative stage, major surgery for organ replacement, extended time of intensive care unit hospitalization, frequent instrumentation, and the net state of postoperative immunosuppression. Studies have shown that the most common sites of infection include surgical site, abdomen, and bloodstream [7,20]. Among these, bacteremia has been a main cause of morbidity and mortality (attributable mortality is approximately 30%) in LT recipients [21].

Yang et al [22] reported that initial inappropriate antibiotic administration or delayed appropriate antibiotic administration were significantly associated with higher mortality rates in patients with BSI. However, while starting antimicrobial treatment for BSI in transplant patients, a dilemma frequently occurs whether or not to initiate immediate therapy targeted to the suspected infecting agent, in a situation when results from conventional identification methods are available only 24 to 48 h after a positive signal. Furthermore, the novel threats currently arising from multi–drug-resistant bacteria have made this dilemma more complex. Therefore, several high-throughput diagnostic tests for rapid identification of bacteria and fungi in positive blood cultures have been developed. These rapid diagnostic tests may be classified as PCR-based, microarray-based platforms, and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) technologies. PCR and microarray-based platforms may identify a limited number of prespecified microorganisms directly from positive blood cultures. Additionally, MALDI-TOF MS systems may only identify microorganisms growing on solid media [7,18].

Recently, FilmArray has been introduced with a relatively wide target spectrum, including common BSI pathogens and a shorter turnaround time. There is only a limited number of studies on the clinical performance of the FilmArray assay; however, available data appear promising. Blaschke et al [23] reported that the FilmArray successfully identifies more than 90% of 201 BSI pathogens, including all culture-proven methicillin-resistant *S aureus* and vancomycin-resistant enterococci. Similarly, Altun et al [9] reported that the FilmArray could identify 153 of 167 (91.6%) BSI pathogens with high sensitivity (for Gram-negatives, 98.5%; for Gram-positives, 96.7%; for fungi, 100%; and for antimicrobial resistance determinants, 96%) and specificity (for Gram-negatives, 100%; for Gram-positives, 93.7%; for fungi, 99.5%; and for antimicrobial resistance determinants, 98.9%). Furthermore, they emphasized that the FilmArray detected additional pathogens in 6 (3.7% of all studied isolates) samples that were formerly classified as having monomicrobial growth with conventional methods. In a recent study, the performance of the FilmArray assay in terms of identification of BSI pathogens before positivity in the blood culture system was investigated, revealing very interesting results [24]. According to that study, the FilmArray assay could identify all isolates in blood culture bottles after 7.5 h of incubation in the device, before a positive signal was released. Furthermore, the authors showed that this assay detected the pathogens in half of the samples before the incubation of the bottles in the device. Therefore, it appears that this assay has the potential to enhance and advance the clinical diagnosis of BSI. However, more studies are needed.

In this study, we evaluated the performance of the FilmArray for diagnosing BSI pathogens in LT patients in a prospective survey. This patient population was of particular importance because of their high vulnerability and susceptibility to bloodstream infections, and they may represent different pathogen profiles than those seen in other patients.

We found that approximately 64.2% of the isolates were Gram-negative and 28.5% were Gram-positive bacteria; only 3 (7.1%) yeast isolates were defined throughout the study. We observed that the FilmArray identified these organisms with high accuracy. The results of this assay for Gram-positive bacteria and yeast completely matched the results of the conventional methods. Discordance between the FilmArray and the standard method was observed in only 2 patient samples both positive for *M morganii*, which is an organism not included in the assay's test panel. On the other hand, it was very surprising that the FilmArray detected additional pathogens in a total of 5 patient samples, 3 of which were classified with monomicrobial growth and the remaining 2 were identified as a skin contamination by the classic identification method. Therefore, we think that the application of FilmArray to samples from critically ill patients would reduce laboratory-based diagnostic issues because of overwork and professional experience.

In this study, Vitek II and Vitek MS could identify all organisms involved. Disagreement between these 2 methods occurred on the non-albicans yeast isolate, which Vitek II identified as *C tropicalis* whereas Vitek MS identified as *C kefyr*.

We observed that the FilmArray was also successful in detecting the 3 resistance determinants. With the disc diffusion antimicrobial susceptibility test and subsequent molecular analysis, 4 staphylococci were found as methicillin-resistant, whereas the remaining 4 were methicillin-susceptible. The results of the FilmArray were in full concordance with these data. In this study, we did not detect any vancomycin-resistant enterococci. Correspondingly, all *VanA/B* gene results of the FilmArray assay were negative. Furthermore, we observed that 6 of all isolated Gram-negative bacteria were carbapenem-resistant; however, the FilmArray assay was not positive for the *KPC* gene in any of the strains. We thought that it could be due to 1 or more of the following reasons: First, there are a number of mechanisms mediating carbapenem resistance among Gram-negatives, including decreasing permeability (outer membrane protein loss), up-regulation of efflux pumps, and production of carbapenem-hydrolyzing beta-lactamases. Furthermore, at least 30 different types of carbapenemases

have been defined to date, and KPC is only one of these enzymes. Second, KPC is originally present in *K pneumoniae*, and expression of this enzyme in other Gram-negative bacteria is limited. Third, OXA-48, IPM, and VIM type carbapenem-hydrolyzing enzymes are prevalent in our country [25–27], whereas KPC is relatively rare. Consequently, we observed that the resistance screening profile of the FilmArray panel is also successful in the case of the staphylococci. Because *MecA* is the major predictor for staphylococcal methicillin resistance, we think that accurate and early detection of this gene would be helpful for regulation of the antimicrobial treatment in LT patients. On the other hand, we could not measure the sensitivity of *VanA/B* detection by the FilmArray assay. Nevertheless, the specificity of this assay was impressive. However, we thought that the *KPC* screening function of this assay came with only a limited benefit because *KPC* is responsible for carbapenem-resistance among a very limited fraction of the carbapenem-resistant Gram-negative pathogens. Therefore, we believe that the resistance screening function of the FilmArray panel will predominantly be helpful in the management of antimicrobial therapy of Gram-positive bacterial BSI, yet these constitute a limited proportion of the BSI pathogens in LT patients.

The most impressive score obtained in this study was the total procedure time for identification of BSI pathogens, which was only a mean of 1.22 h with the FilmArray, a time span approximately one-fifteenth of the time required for conventional methods. Additionally, the total required turnaround time did not change according to the nature of the pathogen. For example, isolation and identification of fungi by conventional methods was generally more time-consuming compared with bacteria. Here we identified 3 yeasts from LT patient blood samples within a mean of 42 h with classic culture and 28 h with Vitek II. These time scores were the lengthiest identification procedures in this study, whereas the FilmArray could give results without any delay.

Approximately 1500 liver transplantations have been performed in our institute to date. Like many other transplantation centers, we have currently adopted immediate microbiological methods for processing samples of transplant patients. For example, a clinical sample of an LT patient is processed without delay at any time of the day. We also routinely used an automated identification system for samples from LT patients to shorten the identification time. Additionally, we used to perform rapid evaluation of the culture mediums (at the 16th h of incubation), with the use of direct Gram staining from the positive bottle. However, application of such processes requires overtime work for staff and more costs. Additionally, it was reported that direct Gram staining from positive bottles [28] and early evaluation of the plates yielded low sensitivity and specificity. Also in this study, we observed that direct Gram staining erroneously classified 5 *A baumannii* strains as Gram-positive coccus, and, in such situations, inappropriate therapy could be administered to such LT patients. Consequently, we think that the FilmArray could assist in reducing work load in microbiology laboratories without reducing the quality of the results.

In conclusion, our results suggested that the FilmArray BCID panel is a promising alternative method for diagnosing BSI pathogens in LT patients, the very short turnaround time probably being the most valuable property of this assay.

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