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ORIGINAL ARTICLE

Rational use of antibiotics and FilmArray technology for rapid identification of bacteremias in a pediatric intensive care unit

Uso racional de antibióticos y tecnología FilmArray para identificación rápida de bacteriemias en unidad de cuidados intensivos pediátrica

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What do we know about the subject matter of this study?

There are many studies in the adult population on the usefulness of rational use of antibiotics programs and rapid tests for the identification of bacteremia in critical patients, however, there are few studies in the pediatric population.

What does this study contribute to what is already known?

This study supports the usefulness of early identification of microorganisms causing bacteremia that, along with the rational use of antibiotics program, allows the treating physician to indicate targeted antibiotic treatments reducing the exposure of empirical antibiotics in critically ill children.

Abstract

Severe infections are the leading cause of admission to pediatric intensive care. The FilmArray BCID panel quickly identifies microorganisms that cause bacteremia. **Objective**: To evaluate if the rapid identification of the microorganisms that cause bacteremia, along with a Rational Use of Antibiotics (RUA) Program, allows optimizing the time of antibiotic therapy in a pediatric hospital. **Patients and Method:** Retrospective study which included 100 patients presenting their first episode of bacteremia, divided into 2 groups of 50 each. The first one was Intervention (FilmArray BCID and RUA program) and the second one was Historical Controls (conventional automated ID/AST). The variables evaluated were the time required for microbial identification, duration of appropriate therapy, and antibiotic de-escalation. **Results:** The groups were comparable in terms of demographic characteristics, focus of infection, and etiology of bacteremia. The average time of microorganisms' identification of the control group was 70.5 hours (IC 95% 65.2-78.6) and 23.0 hours (IC 95% 12.4-26.7) in the intervention one ($p < 0.05$). The average time of targeted therapy onset was shorter in the intervention group (27.9 h [IC 95% 22.3-32.8]) than that of the control one (71.9 h [IC 95%

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63.2-77.8]) ($p < 0.05$). Finally, the time to de-escalate or discontinue antibiotics in the intervention group and the control one was 6.4 hours (IC 95% 2.76-9.49) hours and 22.0 hours (IC 95% 6.74-35.6 h) respectively ($p > 0.05$). **Conclusion:** The FilmArray panel along with the RUA Program allows the identification of the microorganisms causing bacteremia faster than conventional methods, which positions it as a tool that optimizes antibiotic therapy of critical patients.

Introduction

The early identification of microorganisms that cause bacteremia in critical pediatric patients could allow optimization of antimicrobial therapies and favor morbidity and mortality outcomes[1], reducing unnecessary exposure to multiple empirical antibiotics that are mostly broad spectrum and can contribute to increasing both bacterial resistance and the risk of adverse drug events[2,3].

Previously, there were no technological tools available to quickly identify the pathogens causing bloodstream infections, and broad-spectrum empirical antibiotics were administered for 48 to 72 hours, until the responsible pathogen was identified and then directed antibiotic therapy (continue, escalate, de-escalate, or suspend). Worldwide, there is poor implementation of rational use of antibiotics (RUA) programs in pediatrics, exposing them to the mentioned risks, and the untimeliness in the decision making. This situation has improved at present since hospitals have progressively implemented RUA[2] programs.

Currently, several technologies reduce the time to identify the pathogens that cause bacteremia, including the FilmArray® Blood Culture Identification Panel (BCIP) (Biofire, Salt Lake City, United States). However, few pediatric studies evaluate its effectiveness regarding timeliness and accuracy of antibiotic therapy, as well as its impact on clinical outcomes in the bacteremia management.

Available studies, predominantly in adults, highlight the importance of linking rapid identification tests to the rational use of antibiotics, effective communication between the clinical laboratory and treating physicians, and improved timeliness in the interpretation of panel results. These activities contribute to optimal program outcomes and involve previously sensitized and trained health personnel to avoid barriers to implementation. This program should obtain and analyze quality indicators to measure the impact of its implementation in hospital institutions[2,4-6].

In May 2017, the FilmArray BCIP was implemented at the *Hospital Infantil Los Angeles* (HILA). This technology allows the identification of 24 pathogens at the species or genus level (Gram-positive bacteria, Gram-negative bacteria, fungi), and 4 antibiotic resistance genes (VAN A/B, blaKPC, and mecA) around 1 hour after the positivity of blood culture. Our objective was to evaluate if the rapid identification of microorganisms in bacteremia according to the RUA program, allows us to optimize the time of directed antibiotic therapy and antibiotic de-escalation in a Pediatric Intensive Care Unit (PICU) of a high complexity institution.

Patients and Method

Quantitative experimental study conducted at the *Hospital Infantil Los Angeles* (HILA) in Pasto, Nariño, Colombia, where the RUA Program was implemented in 2016. The project was approved by the Ethics Committee of the Hospital on October 9, 2018, and classified as "Low Risk" according to Article 11 of Resolution 8430 of 1993.

We included 100 patients with the first episode of bacteremia, aged between 1 month and 18 years, requiring hospitalization in PICU. The intervention group considered 50 patients in whom all FilmArray BCIP were performed between May 2017 and January 2019, and the control group considered 50 patients with conventional microbiology. These were historical controls included between January 2014 and December 2016, paired for the same species of the identified microorganism.

We excluded patients who died or were referred before the blood culture was reported and those with an incomplete medical history. Reporting biases were controlled by carrying out a comprehensive search of medical records, we standardized the definitions of the variables, created an organized process for the review of the clinical records with coding in the data collection, and conducted a pilot test.

In both groups, blood cultures were performed using Bactec™ Plus Aerobic medium (BD Diagnostics, Franklin Lakes, United States) and Gram staining was performed using the samples of bottles with positive growth, and a subculture in agar, to then identify the microorganisms by automated method Phoenix™ 100 ID/AST (BD Diagnostics, Franklin Lakes, United States). In the intervention group, after the identification of the microorganism by Gram staining, the FilmArray

BCIP was performed according to the manufacturer's indications.

The data were collected from a secondary source (electronic medical records). Clinical and socio-demographic variables, sensitivity, and specificity of the FilmArray test were recorded. Microorganisms were identified by conventional microbiology and FilmArray. The exposure variable was the conventional microbiology technique and the FilmArray technology adapted to the RUA program and the response one was exposure time.

Other covariates were included to adjust the analyses, such as time of microorganism identification by blood culture or by FilmArray (average time in hours from blood culture collection to the microbiology report of blood culture or the FilmArray), targeted therapy time (average time in hours from blood culture collection to administration of correct antibiotic in both groups), and de-escalation time (average time in hours from the microorganism identification by blood culture or FilmArray to the suspension or decrease in the spectrum of an empirical antibiotic that was not the correct one for the cause of the bacteremia). Inappropriate empirical therapy was defined as if antibiotics were administered without knowing the causative germ, but after knowing the result of the FilmArray or blood culture, the physician decides that it was not required or was inappropriate.

Descriptive statistics data analysis expressed in relative and absolute frequencies, graphs for qualitative variables, and mean and standard deviation for quantitative variables. Normality was tested using the Kolmogorov-Smirnov test. To analyze the qualitative and quantitative variables of parametric distribution, we used the Chi-square test and Student's T-test, and the Mann-Whitney U test when the distribution was non-parametric. The tests presented a 95% confidence interval. We used the statistical software SPSS®, version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.)

Results

We included 50 patients in each group, with comparable demographic characteristics, source of infection, and bacteremia etiology. In both groups, bacteremia was predominantly associated with lung infection (Table 1).

Regarding the microbiology, gram-positive cultures account for 50%, gram-negative 49.5%, and fungi 0.5%. 11% of cultures were poly-microbial (11/100), with a tendency to be higher in the intervention group (14%, 7/50). There were no significant differences in the distribution of microorganisms between the groups, the most frequent bacteria were *Staphylococcus aureus*, *coagulase-negative Staphylococcus*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Serratia marcescens* (Table 2).

The average time of microorganism identification was lower in the intervention group than in the control one [23.1 h (95% CI 12.4-26.7) vs 70.5 h (65.2-78.6), $p < 0.05$], as was the average time of targeted therapy administration [27.9 h (95% CI 22.3 h-32.8) vs 71.9 h (95% CI 63.2-77.8 h), $p < 0.05$]. There was a trend towards less time to de-escalate or suspend antibiotics in the intervention group [6.4 h (95% CI 2.76-9.49 vs 6.74-35.6, $p > 0.05$], especially for gram-positive bacteria [2.1 h (95% CI 0.11-3.7) vs 13.1 h (95% CI 3.2-27.4 h, $p > 0.05$) than in gram-negative ones [11.2 h (95% CI 4.0-16.3) vs 32.9 h (95% CI 5.12 h-55.4 h, $p > 0.05$) (Table 3 and Figure 1). In 100% of the intervention group, de-escalation or suspension of antibiotics was initiated after the FilmArray results, unlike the control group, where only occurs in 76%.

FilmArray technology had a sensitivity and specificity of 97.4%, in mono and polyculture (Table 4). There was one case (2%) in which FilmArray did not identify the microorganism causing the bacteremia (*Acinetobacter baumannii*), causing prolonged inappropriate antibiotic therapy.

Discussion

This study showed that the rapid identification of microorganisms causing the bacteremia using the FilmArray BCIP has a positive impact on the implementation of the RUA program in the PICU since the treating physician can target the antibiotic treatment, stop the empirical therapies more quickly, and therefore start appropriate treatments according to the microorganism identified, applying the institutional antibiotic guidelines, which at the same time contributes to reducing exposure to inappropriate antibiotics that can increased bacterial resistance and adverse effects in patients[7,8].

The average identification time observed in the intervention group was 47 hours less than the control one, which is similar to other pediatric studies where the identification time with FilmArray was 42.5 hours less than conventional microbiology[2].

In the intervention group, the decision to switch antibiotics to targeted therapies was on average 44 hours faster and the time to de-escalate antibiotics after knowing the results of the FilmArray was 15 hours less than the control group, decisions made 24/7 by the treating physicians[2].

We believe that the results in reducing the time to decide on targeted therapies and to de-escalate antibio-

Table 1. Sociodemographic and clinical characteristics of children with bacteremia

	Variable	Category	Control Group n = (50)		Intervention Group n = (50)		P-value
			N	%	N	%	
Demographics	Age (years)	< 1	15	30	15	30	0.77
		1 - 5	9	18	14	28	
		6 - 11	10	20	3	6	
		12 - 17	16	32	18	36	
	Sex	Male	30	60	27	54	0.34
		Female	20	40	23	46	
	Race	Mestizo	34	68	31	15.5	0.88
		Afro-descendant	9	18	16	8	
		native	7	14	3	1.5	
Clinics	Days stay M-(DE)		19.8 (31.7)		14.3 (13.9)		0.19
	Admission diagnoses	Lung infection	12	24	17	34	0.82
		Sepsis	10	20	4	8	
		TBI	4	8	2	4	
		Osteoarticular infection	5	10	6	12	
		C. gastrointestinal	8	16	9	18	
		Others	11	22	12	24	
	Type of microorganism	Gram positive	50	100	50	100	0.57
		Gram negative and fungus	50	100	50	100	
		MecA	15	30	15	30	
		Van A/B	0	0	0	0	
		KPC	0	0	0	0	

TBI: Traumatic brain injury; C. Gastrointestinal: Sugery gastrointestinal; MecA: Gene responsable for methicillin resistance; Van A/B: Genetic determinants of glucopeptide resistance; KPC: Carbapenemasa class A, confers resistance to all beta-lactams. *Value of shi2 (value of $p < 0.05$). **Test U de Mann Whitney for non-normal quantitative variables ($P < 0.05$)

tics may be due to the activities carried out as part of the RUA program which includes awareness, training, and personalized feedback of medical and clinical laboratory staff.

It is important to note that FilmArray technology alone does not guarantee the impact reached in this study. The institutions that have this technology must ensure its inclusion as a tool for the RUA Program in order to the physician opportunely knows the results and changes the antibiotic therapy if applicable. In the case of this Institution, it was agreed with the Clinical Laboratory to name the results of the FilmArray as critical, meaning immediate and direct communication with the physician for clinical decision-making[2,5,6,8,9].

Unlike the control group, there was de-escalation or suspension of antibiotics in all patients after the FilmArray result, allowing better use of the antibiotics, which is similar to the study by Ray et al.[4]. After the intervention, there were rapidly targeted therapies, without waiting for the antibiogram result, which means that rapid diagnostic tests helped decision-making based on the identified bacteria[8,10,11].

In addition, there was a decreased use of inappropriate empirical antibiotics[3,12-14], especially in the group of Gram-positive bacteria[15]. We believe that this may be that the resistance genes for gram-positive bacteria analyzed by the test, such as mecA and van A/B, help the physician in making decisions to de-escalate or suspend antibiotics, unlike gram-negative bacteria, since in hospitals with low resistance rates for blaKPC, information on carbapenem resistance is less useful than typing extended-spectrum beta-lactamases (ESBL). The-

Table 2. Comparison of blood culture results with results of FilmArray BCID panel for the identification of microorganisms causing bacteremia of positive poly and monomicrobial cultures

Group	Resultsblood culture Preintervention	n	Filmarray results	n
Gram positives	MRSA	6	MRSA	6
	MSSA	7	MSSA	7
	CoNS	8	CoNS	7
	Streptococcus pyogenes	1	*Streptococcus pyogenes*	1
	Streptococcus pneumoniae	3	*Streptococcus pneumoniae*	3
Gram negatives	*Klebsiella pneumoniae*	6	*Klebsiella pneumoniae*	6
	Acinetobacter baumannii	2	*Acinetobacter baumannii*	1
	Serratia marcescens	1	*Serratia marcescens*	1
	Pseudomonas aeruginosa	2	*Pseudomonas aeruginosa*	2
	Salmonella tiphy	3	*Enterobacteriaceae; salmonella tiphy*	1
	Enterobacter cloacae	1	*Enterobacteriaceae: Salmonella* spp.	1
	Escherichia coli	4	*Escherichia coli*	3
Polymicrobials	*Klebsiella pneumoniae* and *Acinetobacter baumannii*	1 1	*Klebsiella pneumoniae* and *Escherichia coli*	2 2
	Klebsiella pneumoniae and *Sthaphylococcus Cromogenes*	1 1	*Klebsiella pneumoniae* and *Serratia marcescens*	1 1
	Serratia marcescens and *Enterobacter cloacae*	1 1	*Serratia marcescens* and SAMS	2 2
	Serratia marcensens and *Escherichia coli*	1 1	*Enterobacteriaceae: Salmonella* spp y SAMS	1 1
	–	–	*Serratia marcescens* and *Enterobacter cloacae complex*	1 1
Fungus	*Candida albicans*	1	*Candida albicans*	1[a]
Organisms not identified for the panel	*Burkholderia cepacea*	1	*Burkholderia cepacea*	1[a]
	–	–	*Aerococcus viridans*	1[a]
	–	–	*Acinetobacter baumannii*	1[b]

MRSA = Methicillin Resistant *Staphylococcus aureus* MSSA = Methicillin sensitive *Staphylococcus aureus*; CoNS = Coagulase Negative *Staphylococci*; [a]Microorganisms not included in the panel for identification; [b]Microorganisms included in the panel but not identified.

Table 3. Comparison of clinical and laboratory results of children with bacteremia

Group	Variable	Pre-implementation Group n = (50) (IC 95%)	Post-implementation Group n = (50) (IC 95%)	P valor
Laboratory results	Identification time of microorganism by blood culture and Film Array	70,5 (65,2-78,6)	23,0 (12,4-26,7)	0,00*
Clinics results	Start time of targeted therapy	71,9 (63,2-77,8)	27,4 (22,3-32,8)	0,00*
	Time to de-escalate or suspend antibiotics when the microorganism was identified by FilmArray and blood culture	22,0 (6,74-35,6)	6,38 (2,76-9,49)	0,92
	Gram positive	13,1 (3,2-27,4)	2,06 (0,11-3,68)	0,45
	Gram negative	32,9 (5,12-55,4)	11,2 (4,0-16,3)	0,81

*Test U de Mann Whitney for non-normal quantitative variables ($P < 0.05$).

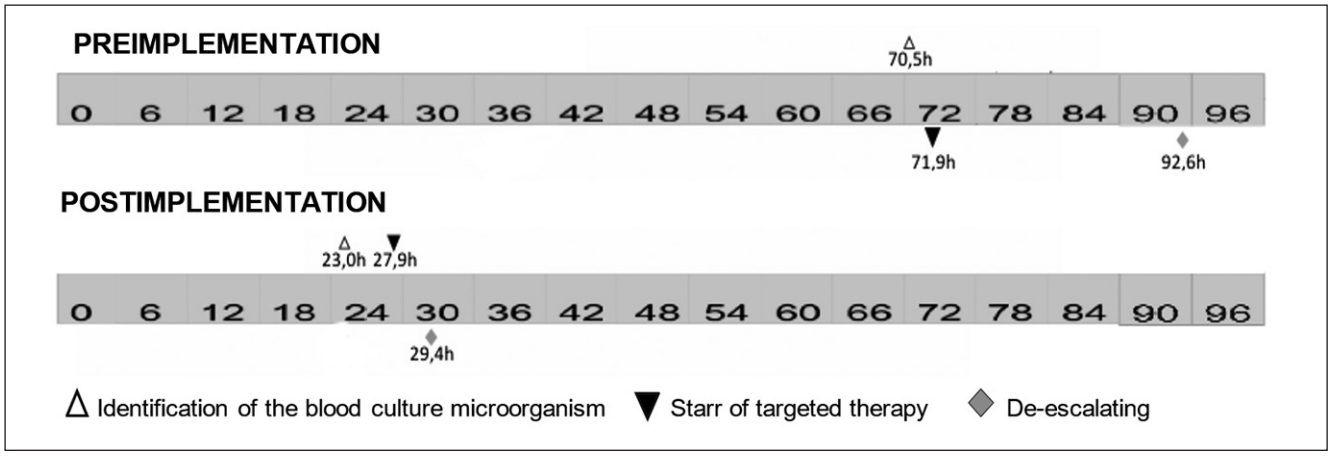

Figure 1. Comparison of clinical and laboratory results of children with bacteremia.

Table 4. Post-test probability, sensitivity and specificity of FilmArray technology for early identification of bacteremias

Estimated pre-test probability	Sensitivity	Specificity	Positive post-test probability. % (IC 95)	Negative post-test probability. % (IC 95)
50.6	97.4	97.4	97.5 (88.8-99.5)	2.7 (0.6-11.6)

refore, the decision to de-escalate carbapenems is subject to analysis of risk factors of patients who may have this type of resistance[16], especially for bacteria such as *Klebsiella spp*., *Pseudomonas spp*., and *Escherichia coli*, decreasing the chances of de-escalating or suspending antibiotics in infections due to this type of bacteria since the risk of inappropriate antibiotic therapy increases negative clinical outcomes in this group of patients[13,17].

The FilmArray BCIP showed in this study high sensitivity and specificity for all 24 pathogens, including polymicrobial cultures with adequate concordance when compared with conventional microbiology[2,7,18-22]. Southern et al.[18] did not identify 8 of the microorganisms present in this panel, reaffirming the adequate sensitivity and specificity for the microorganisms included in the FilmArray BCIP.

Patients who presented bacteremia due to *Salmonella spp*. and *Salmonella typhi* were identified by the panel as *Enterobacteriaceae* and presented delays in starting the directed therapy, evidencing again the importance of the quick identification of the microorganisms causing bacteremia for an adequate choice and duration of the antibiotic treatment.

The sensitivity and specificity in our study for resistance genes were 100% compared with conventional microbiology. These results are similar to the multicenter study by Salimnia et al.[23,24] who found a 98,4% of sensitivity and 98,3% in specificity in mecA, and 100% for van A/B and blaKPC[25,26], which generates confidence in the interpretation of the FilmArray BCIP.

Our study has some limitations typical of a retrospective study. Sociodemographic variables are not controlled as pairs of the same species of the identified germ were considered. Since in the pre-intervention period the RUA program was not implemented, the results obtained in the post-intervention period cannot be generalized for the times of directed therapies and de-escalation or suspension of antibiotics. As it was performed in a single center, the sample was relatively small, thus some of the variables show trends without reaching statistical significance and more patients should be included to confirm them.

Despite this, we would like to emphasize that this is one of the few studies carried out in a pediatric population in Latin America that evaluates the effectiveness of FilmArray BCIP for the identification of bacteremia, and which shows the advantages of having this test along with activities of rational use of antibiotics.

In conclusion, the FilmArray technology is a useful tool, which contributes in RUA programs to decision making in critically ill patients with bacteremia, and which allows us to quickly identify causative microorganisms with high sensitivity and specificity, generating confidence in decision making regarding antibiotic treatment adjustments, allowing the physician to formulate targeted antibiotic therapies and decreasing

patient exposure to inappropriate empirical antibiotics.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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