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ORIGINAL ARTICLE

Clinical Impact and Provider Acceptability of Real-Time Antimicrobial Stewardship Decision Support for Rapid Diagnostics in Children With Positive Blood Culture Results

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Background. Rapid diagnostic technologies for infectious diseases have the potential to improve clinical outcomes, but guideline-recommended antimicrobial stewardship (AS) strategies are not currently optimized for rapid intervention. We evaluated the clinical impact and provider acceptability of implementing real-time AS decision support for children with positive blood culture results according to the FilmArray blood culture identification panel (BCID [BioFire Diagnostics]) at Children's Hospital Colorado.

Methods. A pre-post quasi-experimental design was used to compare the outcomes of 100 postintervention children with positive blood culture results matched with 200 preintervention control children. Causative organisms in the preintervention group were identified using conventional microbiologic techniques and communicated to providers by a microbiology technologist. Postintervention organisms were identified by the BCID and communicated by an AS provider in real time with interpretation and antimicrobial recommendations. The primary outcome was time to optimal antimicrobial therapy (time from blood culture collection to start of predetermined pathogen-specific regimen or antimicrobial discontinuation for contaminants) compared by a log-rank test and Kaplan–Meier analysis. Provider acceptability of the intervention was assessed via E-mailed surveys.

Results. The median time to optimal therapy decreased from 60.2 hours before intervention to 26.7 hours after intervention (P = .001). Among children with blood cultures that contained true pathogens, the time to effective antimicrobial therapy decreased from 6.9 to 3.4 hours (P = .03). Unnecessary antibiotic initiation for children with a culture that contained organisms considered to be contaminants decreased from 76% to 26% (P < .001). Providers reported a change in management as a result of BCID results in 73% of the cases and a mean overall satisfaction rating of 4.8 on a 5-point Likert scale.

Conclusions. Real-time AS decision support for rapid diagnostics is associated with improved antimicrobial use and high satisfaction ratings by providers.

Keywords. antimicrobial stewardship; bloodstream infections; outcomes; rapid diagnostics.

INTRODUCTION

Rapid identification of a causative organism is essential for providing effective targeted antimicrobial therapy to children with a serious infection [1]. New rapid molecular diagnostic technologies for infectious diseases enable expedited and accurate microbiologic diagnoses [2]. However, prompt appropriate clinical action is required to translate these faster test results into improved patient care. Without proper clinical support, rapid diagnostic test results can lead to provider confusion, practice variability, and suboptimal clinical impact [1, 3]. Effective implementation strategies and ongoing support for rapid infectious disease diagnostics are needed to ensure diagnostic and antimicrobial stewardship so that these new technologies conserve, rather than consume, healthcare resources [4].

Antimicrobial stewardship (AS) programs have been designed to guide the appropriate use of antimicrobials [5, 6]. However, guideline-recommended AS strategies, including prior authorization, formulary restriction, and prospective audit with feedback [7], are not individualized to specific patient situations or do not occur when rapid diagnostic results are first available. Real-time AS decision support provides rapid diagnostic microbiologic test results with interpretation and antimicrobial recommendations at the time of medical decision

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making. The clinical effectiveness of this type of rapid diagnostic AS intervention in the pediatric setting and the acceptability of unsolicited expert advice to providers are unknown.

Bloodstream infections (BSIs) are the second leading cause of severe sepsis in children and are associated with 20 000 to 75 000 hospitalizations, more than 4,000 deaths, and more than $4.8 billion in healthcare costs annually in the United States [8–10]. Conventional microbiologic techniques currently take a median of 15 hours to provide a positive blood culture result and more than 72 hours to identify the organism(s) [2]. Delayed organism identification in BSIs can postpone the administration of effective antimicrobial therapy, which increases morbidity and death. It also can lead to an overuse of broad-spectrum empiric antimicrobials, which increases unnecessary healthcare resource utilization and antimicrobial resistance [11–14]. The FilmArray blood culture identification (BCID) panel (BioMérieux, BioFire Diagnostics, Salt Lake City, UT) uses automated real-time multiplex polymerase chain reaction technology to identify nucleic acid sequences of 24 pathogens and 3 antimicrobial resistance genes associated with BSIs within 1 hour of growth in a blood culture bottle confirmed by Gram stain (Supplement 1) [15]. The BCID panel and similar rapid diagnostic systems for blood culture identification can decrease the time to organism identification significantly [16–19], but maximizing their ability to actually improve outcomes will require systems for prompt and effective communication of results. In this study, we investigated the clinical impact and provider acceptability of implementing real-time AS decision support with the BCID panel for children at Children's Hospital Colorado (CHCO) with a positive blood culture result.

METHODS

Study Design

A pre-post quasi-experimental design was used to compare the outcomes of 100 children with a positive blood culture result after implementation of the BCID panel and a real-time AS decision-support intervention (January to March 2015) matched with 200 children before the intervention (2010–2014). All first positive blood culture results from children who presented to CHCO were included. Repeat BSIs during the same hospitalization were excluded. Preintervention control children were matched 2 : 1 with children after the intervention and grouped by age (<2 months, 2–6 months, 6 months to 3 years, or >3 years), blood culture source (peripheral, temporary central catheter, or fixed central catheter), immune status (immunocompromised or immunocompetent), and pathogen type (Gram-positive bacterium, Gram-negative bacterium, yeast, or mixed).

Laboratory Methods

In both the preintervention and intervention periods, blood culture bottles (Plus Aerobic/F and PedsPlus/F [Becton Dickinson and Co, Sparks, MD]) were incubated in a BacTec 9120/9240 automated system (Becton Dickinson and Co) until identified as positive or for 5 days. Gram staining was performed promptly on all positive bottles. In the intervention period, the BCID panel was used according to manufacturer instructions after the organism(s) was visualized by Gram staining. In both periods, organisms were subsequently identified, and susceptibility testing was performed using conventional methods (Supplement 2).

Reporting Methods

In both periods, Gram stain results on the first positive blood cultures were reported to providers by a microbiology technologist within 30 minutes. During the intervention period, a microbiology technologist communicated the BCID results directly to a member of the AS team, which consisted of 3 infectious disease physicians and 2 infectious disease pharmacists, via pager Monday through Friday 6 AM to 6 PM (Figure 1). The AS provider then reviewed the patient's electronic medical record and called the provider who was caring for the patient with BCID results, interpretation, and antimicrobial recommendations. Consensus pathogen-specific antimicrobial recommendations, based on national guidelines and local antibiogram data, were created to standardize AS recommendations [20]. Results obtained during the night and on weekends were called directly to the provider by the microbiology technologist and reviewed the next weekday morning by an AS team member. Infectious disease consultation was recommended in complicated cases that required more than a cursory chart review.

Data Collection and Analysis

Clinical and laboratory data were collected from the electronic medical record in a standardized Research Electronic Data Capture (REDCap) database [21]. Performance of the BCID panel during the intervention period, including pathogens

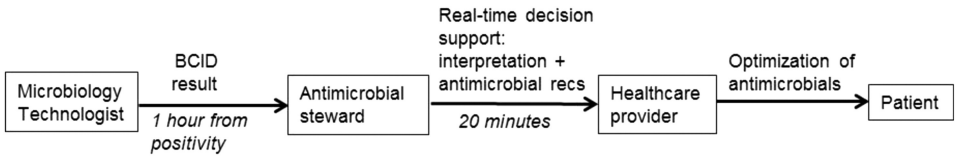

Figure 1. Real-time antimicrobial stewardship decision-support intervention design.

detected and time to identification, was compared to concurrent conventional blood culture identification. The primary study outcome was time to optimal antimicrobial therapy, defined as the time from blood culture collection to the initiation of a predetermined pathogen-specific antimicrobial regimen. For polymicrobial cultures, this process required the initiation of predetermined pathogen-specific antimicrobials to cover each organism identified, and no distinction was made for the number of antimicrobials used. Given the lack of consensus on objective criteria for differentiating blood cultures that contain organisms considered contaminants from true pathogens, clinical determination by the medical team was used to make this differentiation [22]. This differentiation required discontinuation of antimicrobials targeting the BSI with the reason for discontinuation documented in the electronic medical record as interpretation of culture as a contaminant. The time to optimal antimicrobial therapy for a blood culture clinically determined to be a contaminant was defined as the time until antimicrobial discontinuation. Secondary outcomes included time to effective antimicrobial therapy (time of blood culture collection to initiation of an antimicrobial to which the organism was either found or predicted to be susceptible according to Clinical Laboratory Standards Institute criteria), antimicrobial hours, length of stay, and death. Antimicrobial hours were calculated by adding the time from the first dose to the last dose of each antimicrobial targeting the BSI (eg, 48 hours of vancomycin and 24 hours of concurrent ceftriaxone = 72 antimicrobial hours). For those admitted to the hospital, the length of stay after a positive blood culture result was calculated from the date of collection of blood for culture or the date of admission (whichever was later) to the discharge date. BSI-related death was defined as death during the hospitalization for BSI attributable to a BSI-related complication.

Categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were log transformed, if necessary, and compared using 2 sample t-tests. The time-to-outcome variables were compared using a log-rank test and Kaplan–Meier analysis. The Wilcoxon rank-sum test was used to compare time to infectious disease consult due to skewness. Statistical analysis was conducted using R 3.1.1 software with a .05 confidence level. Initial power analysis calculated a sample size of 400 children matched with 800 controls to provide 90% power to detect in 6 hours a difference in time to optimal therapy based on preliminary data. However, preliminary analysis of the first 100 intervention children matched with 200 controls revealed a significant difference in the primary outcome, and the study was stopped prematurely.

An electronic REDCap study survey was e-mailed to all providers who had received the real-time AS decision support within 2 weeks of the intervention [21]. Survey respondents characterized perceived changes in management of their patient with a positive blood culture result caused by BCID results and rated their opinion of the real-time AS intervention by scoring its perceived accuracy, timeliness, and respect for autonomy on a 5-point Likert scale (ranging from 1 [very unsatisfied] to 5 [very satisfied]). Descriptive statistics were used to summarize survey responses.

This study was deemed nonhuman subjects research after review by the CHCO Organizational Research Risk and Quality Improvement Review Panel.

RESULTS

Study Population

A total of 100 cases during the intervention period were compared with 200 matched controls during the preintervention period. Patient characteristics, including age, sex, race, and ethnicity, were similar between the 2 groups (Table 1). A majority of the children had an underlying medical condition (71% in the intervention group vs 60% in the preintervention group; $P = .08$), and 19% in each group were immunocompromised ($P = 1$). There were no differences in the distributions of blood culture

Table 1. Patient and Culture Characteristics of Children With a Bloodstream Infection in the Preintervention and Intervention Periods

Variable	Preintervention Group (N = 200)	Intervention Group (N = 100)	*P* Value
Patient characteristics			
Age (geometric mean [95% CI])	2.7 (2–3.5)	2.4 (1.6–3.6)	.68
<2 mo (n [%])	30 (15)	15 (15)	1
2–6 mo (n [%])	20 (10)	10 (10)	
6 mo to 3 y (n [%])	32 (16)	16 (16)	
>3 y (n [%])	118 (59)	59 (59)	
Male sex (n [%])	117 (58)	62 (62)	.65
Nonwhite race (n [%])	38 (21)	17 (20)	.89
Hispanic/Latino ethnicity (n [%])	58 (30)	26 (28)	.78
Underlying medical condition (n [%])	119 (60)	71 (71)	.08
Immunocompromised	38 (19)	19 (19)	1
Culture characteristics			
Source of specimen (n [%])			.99
Fixed central line	57 (28)	29 (29)	
Temporary central line	21 (10)	10 (10)	
Peripheral	122 (61)	61 (61)	
Organism type (n [%])[a]			1
Gram-positive bacterium (n [%])	146 (73)	73 (73)	
Gram-negative bacterium (n [%])	41 (20)	20 (20)	
Yeast (n [%])	3 (2)	2 (2)	
Mixed types (n [%])	10 (5)	5 (5)	
Clinically considered a contaminant (n [%])	70 (35)	43 (43)	.137

Abbreviations: CI, confidence interval.

[a]See Supplemental Table 1 for species-specific breakdown of organisms detected.

Table 2. Comparison of Laboratory and Clinical Outcomes of Children With a Bloodstream Infection in the Preintervention and Intervention Periods

Variable	Preintervention Group (n = 200)	Intervention Group (n = 100)	*P* Value
Laboratory outcome			
Time to identification (median [95% CI]) (h)	65.4 (62.6–69.1)	22.9 (18.8–26.6)	<.0001[a]
Clinical outcomes			
Time to optimal antimicrobial therapy (median [95% CI]) (h)	60.2 (50.3–73)	26.7 (3.8–44.4)	.001[a]
Death (n [%])	4 (2)	2 (2)	.7821
Blood cultures with an organism considered a true pathogen	*n = 130*	*n = 57*	
Time to effective antimicrobial therapy (median [95% CI]) (h)	6.9 (2–13.1)	3.4 (1.7–6.8)	.03*
Time to antimicrobial therapy (median [95% CI]) (h)	72.4 (49.3–86.2)	48.7 (32.7–65.2)	.004*
Antimicrobial hours (median geometric mean [95% CI])	475.3 (411.4–549)	367.2 (296.1–455.4)	.03
Length of stay after positive blood culture (geometric mean [95% CI]) (days)	10.6 (9–12.5)	14.4 (11.3–18.3)	.06
Blood cultures with an organism considered a contaminant	*n = 70*	*n = 43*	
Unnecessary antimicrobial initiations (n [%])	53 (76)	11 (26)	<.001
Time to discontinuation of antimicrobials among those initiated (geometric mean [95% CI])	51.5 (41.4–64.1)	42 (24.7–71.4)	.5
Unnecessary vancomycin initiations (n [%])	39 (56)	6 (14)	<.001
Time to discontinuation of vancomycin among those initiated (geometric mean [95% CI]) (h)	43.3 (32.7–57.3)	41 (18.9–88.9)	.8
Length of stay after positive blood culture among those admitted (geometric mean [95% CI]) (days)	7 (5.4–9.1)	9.2 (6.3–13.4)	.3

[a]The *P* value was calculated from log-rank time to event analysis.

source or organism types between the groups (Supplement 3). The proportions of cultures considered to be contaminants were also similar in the preintervention and intervention groups (35% vs 43%, respectively; $P = .14$).

BCID Panel and AS Intervention Performance

The BCID panel identified the organism(s) in 84% of positive blood cultures in the intervention period in a median time of 82 minutes (interquartile range [IQR], 72–97 minutes) after blood culture bottles became positive. The BCID panel identified the same organisms as cultures except that it detected 1 *Enterococcus* species in the blood of a pretreated child with Gram-positive cocci in chains that did not grow in culture. Thirteen (13%) positive blood cultures were attributable solely to organisms not included on the BCID panel. Three (3%) children had an organism present on the BCID panel that grew in culture but was not detected by the BCID panel (non-*aureus Staphylococcus*, n = 1; *Salmonella typhimurium* [Enterobacteriaceae], n = 1; and alpha-hemolytic *Streptococcus* [*Streptococcus* species], n = 1). The BCID panel correctly identified all pathogens present on the panel in 13 polymicrobial cultures, although 6 organisms were present in polymicrobial cultures that are not included in the BCID panel.

The median time to organism identification was 42.5 hours less in the intervention period than in the preintervention period ($P < .001$) (Table 2). During the intervention period, the real-time AS decision-support intervention occurred a median of 10 minutes (IQR, 3–19 minutes) after BCID results were reported to the AS team.

Clinical Outcomes

The median time to optimal antimicrobial therapy decreased from 60.2 hours in the preintervention period to 26.7 hours in the intervention period ($P = .001$) (Table 2; Kaplan–Meier curves in Figure 2). The BSI-related mortality rate was unchanged at 2% in both groups ($P = .78$).

Among children with a culture that contained an organism considered to be a true pathogen, during the intervention period, the time to effective antimicrobial therapy decreased from a mean of 6.9 hours to 3.4 hours ($P = .03$), and the time to optimal antimicrobials decreased from a mean of 72.4 hours to 48.7 hours ($P = .004$; Table 2). In this group, the duration

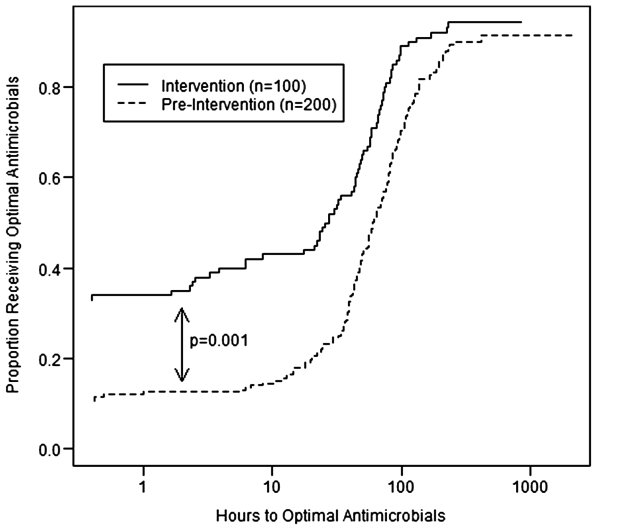

Figure 2. Kaplan–Meier analysis of time to optimal antimicrobial therapy in children with a bloodstream infection in the preintervention and intervention groups. Shown are Kaplan–Meier curves of the proportion of children with a bloodstream infection at CHCO receiving optimal antimicrobials, as defined by predetermined organism-specific consensus guidelines. Cases in the intervention period (2015; n = 100) are represented by the solid line, and matched preintervention (2010–2014; n = 200) controls are represented by the dotted line. Patients not treated with optimal antimicrobials were censored at the time of hospital discharge.

of antimicrobials administered decreased from a mean of 475.3 to 367.2 (P = .03) hours postintervention. The mean length of stay after a positive blood culture result was 10.6 days in the preintervention group and 14.4 days in the intervention group (P = .06).

Among children with a blood culture that grew an organism considered to be a contaminant, the initiation of unnecessary antimicrobials decreased from 76% to 26% (P < .001) and initiation of vancomycin decreased from 56% to 14% (P < .001; Table 2). The mean time to discontinuation among children unnecessarily started on antimicrobials was 51.5 hours before the intervention and 42 hours after intervention (P = .5). In a subanalysis of children who were outpatient when their blood culture became positive for an organism ultimately considered a contaminant, 53.3% were unnecessarily called back to the emergency department in the preintervention period compared to 20% after the intervention (P = .13), and 33.3% were unnecessarily admitted to the hospital compared to 13.3% after the intervention (P = .39). Among children admitted to the hospital with a positive blood culture considered a contaminant, the median length of stay was 7 days in the preintervention group and 9.2 days in the intervention group (P = .3).

In the preintervention period, 32% of the admitted children with a positive blood culture result had an infectious disease consultation compared to 42% of children in the postintervention group (P = .15). There was no difference in days from positive culture result to first consult note between periods (1 day [IQR, 0–3] before intervention vs 1 day [IQR, 1–3] after intervention; P = .7).

Provider Surveys

Surveys were e-mailed to 83 providers of children with a positive blood culture result at CHCO who received a real-time AS decision-support intervention, and 41 responses were received (49% response rate). The departments and positions of survey respondents were representative of the overall distribution of providers at CHCO caring for children with a positive blood culture result and did not differ significantly from those of the nonrespondents. Seventy-three percent of the respondents reported a change in management based on the real-time AS decision-support intervention; 36% narrowed antimicrobial use, 17% expanded antimicrobial use, and 10% avoided unnecessary return visits (Figure 2). Overall provider satisfaction with the real-time AS decision-support intervention was a mean of 4.8 on the 5-point Likert scale, with a mean score of 4.7 for timeliness, 4.7 for respect for provider autonomy, and 4.7 for appropriateness of recommendations. There were no adverse safety events reported, and 41 (100%) of 41 respondents agreed that the real-time AS decision-support intervention program should continue.

DISCUSSION

Our study found that implementation of a rapid organism-identification technology combined with a real-time AS decision-support intervention was associated with improved antimicrobial use in children with a positive blood culture result. Antimicrobial regimens were optimized 33 hours faster, effective antimicrobial therapies for BSI were started 3 hours earlier, and antimicrobial initiations for contaminant cultures were decreased from 76% to 26%. The unsolicited AS intervention received high provider satisfaction ratings and was not perceived to delay result reporting or to encroach on provider autonomy. This approach provides an alternative model for pediatric infectious disease and AS providers to improve clinical care and conserve healthcare resources that could be readily replicated for other rapid diagnostic technologies.

This prospective study in the clinical setting of a children's hospital confirms that the BCID panel can detect organisms in the majority of positive blood cultures, which can lead to significant reductions in time to organism identification. The 84% rate of detection in our pediatric population is comparable to the 81% to 92% of organisms detected by the BCID panel in published pediatric and adult studies [15, 23–26]. In our study, the BCID panel identified all organisms on the panel in polymicrobial cultures, in contrast to a previous study in which only 71% of panel organisms were detected [25]. The on-demand (24 hours/day, 7 days/week) BCID testing at the time of culture positivity conducted in this study led to a median turnaround time of 1.37 hours (IQR, 1.2–1.62 hours), compared to an adult study that used the BCID panel once daily on weekdays and had a turnaround time of 7.4 hours (IQR, 2.6–12.3 hours) [27].

In this study of pediatric patients, clinical impact was most evident for children with a contaminant culture result, which contrasts with results of studies in adult populations in which large impacts on length of stay, mortality rate, and healthcare costs were driven by more rapid identification of Gram-negative and resistant organisms [28, 29]. Contaminated blood cultures are a significant source of unnecessary resource utilization and healthcare costs in children [11, 30, 31]. Although the overall contamination rate of blood cultures in our hospital remained low (1.1%–1.9%), the large number of cultures obtained and the low incidence of true BSI led to more than one-third of positive blood cultures in our study being considered contaminants. The earlier identification and intervention for contaminant cultures led to significant decreases in unnecessary initiations of antimicrobials and fewer unnecessary return emergency department visits and hospital admissions.

AS intervention has been used to enhance the clinical impact of implementing rapid blood culture diagnostic technologies [19, 23, 27–29, 32]. Various AS strategies have been attempted, but to date, real-time AS decision support is the only strategy that has been optimized to provide individualized

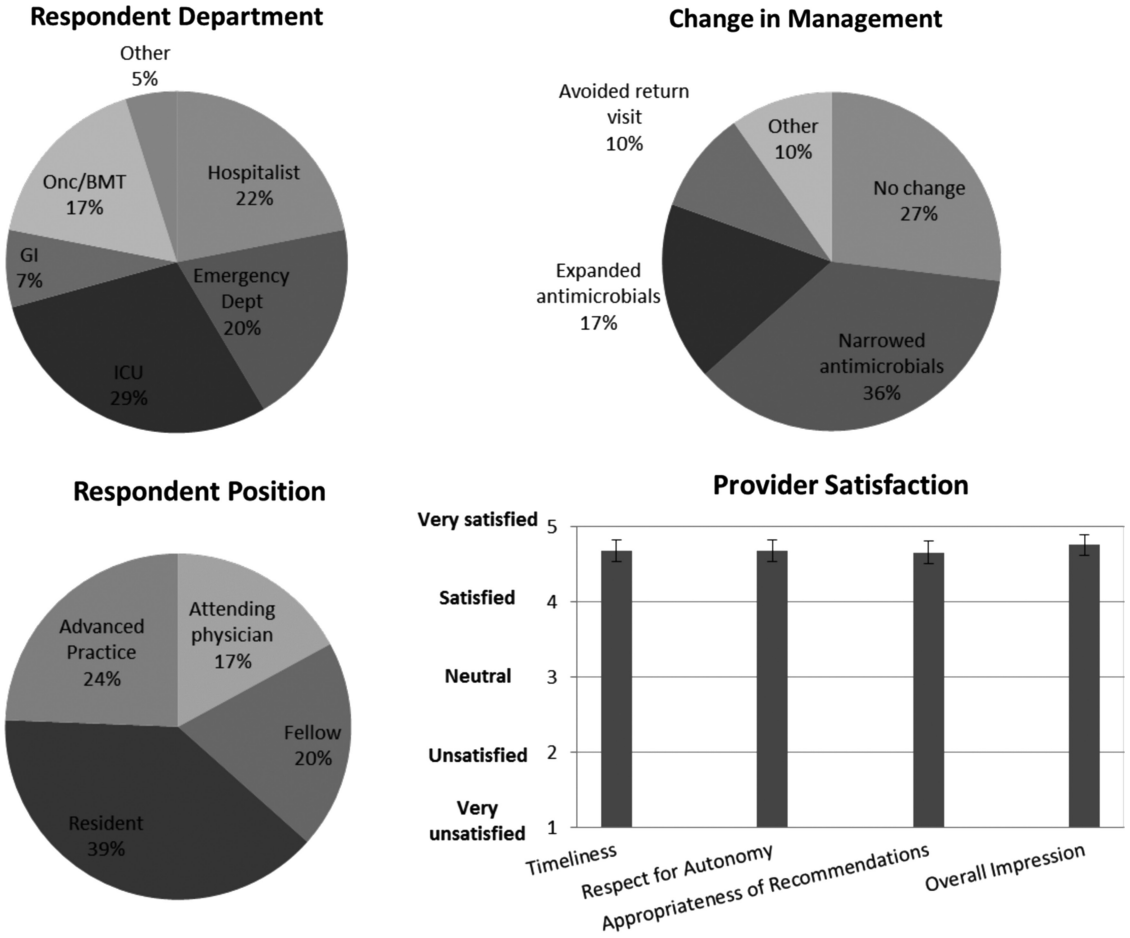

Figure 3. Provider satisfaction with real-time antimicrobial decision support for rapid blood culture identification technology in children with a positive blood culture result. Abbreviations: Onc/BMT, oncology/bone marrow transplant; GI, gastroenterology; ICU, intensive care unit.

intervention at the time of rapid diagnostic results. Formulary restrictions and prior authorization strategies create blanket restrictions on certain antimicrobials but fail to impact the use of medications not on restriction lists [33]. Prospective audit and feedback is typically performed at specified time points (ie, 24 to >72 hours) after the initiation of antimicrobials, rectifying errors after medical decision making has already occurred [34–36]. In contrast, real-time AS decision support incorporated into result reporting intervenes with providers at the time of medical decision making. A recent randomized trial of this real-time AS intervention strategy with the BCID panel decreased time to antimicrobial deescalation by 13 hours compared to the BCID panel with templated reporting comments and by 17 hours compared to conventional blood culture processing alone in adults ($P < .001$) [23]. Our study results affirm the effectiveness and reveal the feasibility of this combined approach in a tertiary care children's hospital. On average, AS providers received 1 to 2 BCID results per weekday, which took less than 15 minutes each to review, intervene, and document. This minimal investment of AS resources capitalizes on the investment made in implementing rapid diagnostic technologies.

Despite the unsolicited nature of our AS intervention incorporated into microbiology result reporting, provider surveys found uniform acceptance and high satisfaction ratings across all departments and provider types. The personal interaction between AS team members and providers using the "handshake-stewardship" approach we developed allows for a 2-way dialogue to individualize recommendations by adapting templated recommendations to specific patient situations [37]. The high ratings of "respect for provider autonomy" confirm the acceptance of our approach. This strategy provides a new opportunity for earlier involvement of AS and does not supplant infectious-disease consultation. Communicating test results through an AS intermediary did not significantly delay result reporting, either objectively (as evidenced by the 10-minute time from result to intervention) or subjectively (as evidenced by the high ratings for "timeliness of intervention" on the provider surveys). The successful pilot of real-time AS decision support for rapid blood culture diagnostics in pediatrics paves

the way for extending this intervention to other rapid diagnostic tests in other clinical scenarios.

The pre-post quasi-experimental design of this study has inherent strengths and limitations. Use of a historical control group enabled more objective quantification of clinical impact than have previous pediatric studies [38], although a pre-post evaluation can be confounded by concurrent non–intervention-associated improvements. In our study, the BCID panel and real-time AS decision-support intervention were introduced simultaneously hospital-wide to provide a standardized implementation strategy with consistent processes across the institution; these processes could be reproduced at other tertiary care children's hospitals. As such, our design does not allow differentiation of the clinical impact caused by the rapid diagnostic test from the AS intervention, although the results of previous studies suggest that a combined approach is more effective [23]. Because of the practical constraint of only providing real-time AS decision support weekdays from 6 AM to 6 PM, the true impact of this approach was likely underestimated in this study.

In conclusion, implementation of the BCID panel in conjunction with a real-time AS decision-support intervention is associated with improved antimicrobial use in children with a positive blood culture result and high satisfaction ratings by providers of all practice types at a pediatric tertiary care hospital. Real-time AS intervention coupled with the implementation of rapid diagnostic technologies translates rapid test results in the laboratory to rapid optimization of antimicrobial therapy at the bedside. Future studies should evaluate the generalizability of our approach to other children's hospitals and application to other emerging rapid diagnostics for additional medical conditions. The emergence of new rapid diagnostic technologies for infectious diseases creates a new opportunity for pediatric infectious disease practitioners to design and implement strategies for improving diagnostic and antimicrobial stewardship.

Supplementary Data

Supplementary materials are available at Journal of *the Pediatric Infectious Diseases Society* online.

Notes

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