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Original Article

Clinical outcomes associated with blood-culture contamination are not affected by utilization of a rapid blood-culture identification system

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Abstract

Objective: Contaminated blood cultures result in extended hospital stays and extended durations of antibiotic therapy. Rapid molecular-based blood culture testing can speed positive culture detection and improve clinical outcomes, particularly when combined with an antimicrobial stewardship program. We investigated the impact of a multiplex polymerase chain reaction (PCR) FilmArray Blood Culture Identification (BCID) system on clinical outcomes associated with contaminated blood cultures.

Methods: We conducted a retrospective cohort study involving secondary data analysis at a single institution. In this before-and-after study, patients with contaminated blood cultures in the period before PCR BCID was implemented (ie, the pre-PCR period; n = 305) were compared to patients with contaminated blood cultures during the period after PCR BCID was implemented (ie, the post-PCR implementation period; n = 464). The primary exposure was PCR status and the main outcomes of the study were length of hospital stay and days of antibiotic therapy.

Results: We did not detect a significant difference in adjusted mean length of hospital stay before (10.8 days; 95% confidence interval [CI], 9.8–11.9) and after (11.2 days; 95% CI, 10.2–12.3) the implementation of the rapid BCID panel in patients with contaminated blood cultures ($P = .413$). Likewise, adjusted mean days of antibiotic therapy between patients in pre-PCR group (5.1 days; 95% CI, 4.5–5.7) did not significantly differ from patients in post-PCR group (5.3 days; 95% CI, 4.8–5.9; $P = .543$).

Conclusion: The introduction of a rapid PCR-based blood culture identification system did not improve clinical outcomes, such as length of hospital stay and duration of antibiotic therapy, in patients with contaminated blood cultures.

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Bloodstream infections are a leading cause of morbidity, mortality, and increased healthcare costs.[1,2] Early recognition of the causative agent and appropriate antibiotic therapy are needed for adequate management of bloodstream infections.[1–4] However, 0.6%–6% of all blood cultures in the United States are contaminated with commensal skin organisms.[5–7] Contamination of blood cultures often results in extended hospital stay and unnecessary use of broad-spectrum antibiotics.[6–8]

The conventional method of identifying microorganisms in blood cultures and providing antimicrobial susceptibility information can take up to 48–72 hours.[9] Recently, several new approaches have been explored for early identification of microorganisms and detection of resistance genes in blood-culture specimens.[4,9] Rapid comprehensive panel-based molecular assays using the polymerase chain reaction (PCR) technique, such as the FilmArray Blood Culture Identification (BCID) panel (bioMérieux, Salt Lake City, UT),[10] can detect many major bloodstream pathogens and selected antimicrobial resistance genes in positive blood cultures.[11–13] Because clinicians receive PCR blood culture testing results within a few hours of a blood culture yielding microbial growth, some data suggest that using rapid diagnostic testing, particularly when coupled with robust antimicrobial stewardship efforts, can decrease mortality, length of hospital stay, duration of antibiotic therapy, as well as, the economic burden associated with bloodstream infections.[14,15]

However, there is limited and conflicting evidence on the impact of rapid molecular diagnostic testing on clinical outcomes of contaminated blood cultures. Pardo et al[16] demonstrated that using PCR to detect blood pathogens led to a statistically significant shorter duration of hospital stay (2.3 days) compared to the control group before the PCR intervention (2.9 days; $P = .008$) in patients who were discharged within 6 days of a contaminated blood-culture result.[16] However, they reported that the duration of antibiotic therapy did not significantly differ between the 2 groups. When comparing periods before and after PCR was implemented, MacVane et al[17] found the median length of hospital stay to be 8 days versus 7 days ($P = .75$) and antibiotic therapy duration with vancomycin to be 1.3 versus 1.7 days ($P = .28$) in patients with contaminated blood cultures.[17] Cattoir et al[18] analyzed 154 episodes of contaminated blood cultures and reported that

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17% of those in the PCR testing group were given unnecessary antibiotics compared to 10% patients in the conventional testing group (OR, 1.77; 95% CI, 0.62–5.12; $P = .237$).

Insufficient data are available on the impact of rapid blood culture testing on clinical outcomes of patients with contaminated blood cultures. Therefore, we assessed the impact of rapid blood culture testing on the length of hospital stay (LOS) and the duration of antibiotic therapy in patients with contaminated blood cultures.

Methods

Study setting

We conducted a retrospective cohort study involving secondary analysis of data extracted from hospital medical records at a single institution. This study was reviewed and approved by the University of Nebraska Medical Center Institutional Review Board. The study population included all adult patients who had blood culture(s) during an admission. The multiplex PCR FilmArray Blood Culture Identification (BCID) panel, was introduced at our institution in November 2013.[10] Following introduction of the BCID, clinicians were alerted of a positive blood culture and Gram-stain characteristics by telephone, which was followed by updated BCID information via the electronic medical record. Electronic medical records of patients with a date of admission between January 1, 2012, and June 30, 2013, were included in pre-PCR group and patients with a date of admission between June 1, 2014, and December 31, 2016, were included in the post-PCR group. Data were not available for July 2012 of the pre-PCR period.

Hospital admissions of patients aged ≥18 years and those who fit the study definition of a contaminated blood-culture episode were included. Participants who were discharged from the emergency department were not included; however, patients who were initially treated in the emergency department and subsequently admitted to the hospital were included. Only the first admission was included in the study sample if a patient had >1 eligible admission during the study period.

Study definitions

Contaminated blood culture. A blood culture was considered contaminated if skin-residing organism(s) were identified in 1 of the 2 (or more) blood-culture sets. The skin-residing organisms include coagulase-negative staphylococci (CoNS), *Cutibacterium acnes*, *Micrococcus* spp, viridians group streptococci (VGS), *Corynebacterium* spp, and *Bacillus* spp. Patients with only a single blood culture obtained were excluded.

Contaminated episode

A patient admission was categorized as a contaminated episode if the first ordered blood culture was reported as contaminated (based on the aforementioned definition of contaminated blood culture) and any subsequent blood culture was negative during the same admission.

Study size

The pre-PCR group with 305 contaminated blood-culture episodes and the post-PCR group with 464 contaminated blood culture episodes comprised the final analytical sample (n = 769) of the study.

Variables

The primary independent variable was PCR status (before or after) depending on whether PCR was used to detect pathogens in blood. To assess the potential impact of sociodemographic variables on outcomes, certain variables were included in the analysis. These variables were age categorized in quartiles (<50 years, 50–61 years, 62–73 years, >73 years), sex (male or female), race (white, black, or other), body mass index (BMI; kg/m^2), smoking status (smoker or nonsmoker), alcohol status (drinks alcohol or does not drink alcohol), marital status (single, married), and medical insurance (insured or uninsured). We also controlled for underlying diseases that have been shown to affect duration of hospitalization and antibiotic therapy in patients with contaminated blood cultures. These underlying diseases were extracted from *International Classification of Disease, Tenth Revision* (ICD-10) codes listed in the electronic medical records of each patient admission and included chronic obstructive pulmonary disease (yes or no), chronic kidney disease (yes or no), liver cirrhosis (yes or no), and diabetes mellitus (yes or no). Some hospitalization-related variables, such as stay in intensive care unit (ICU) during admission (yes or no), admission from emergency department (yes or no) were also included. Finally, to control for the impact of seasonal variation on study outcomes between the 2 periods, we created a variable reflecting the 4 seasons. Patients were assigned to this variable based on date of admission and the effect of seasonality was tested against both outcomes before and after PCR BCID was implemented.

Outcomes

The study had 2 outcomes. The primary outcome was length of hospital stay (in days) and the secondary outcome was duration of antibiotic therapy (in days). Antibiotic therapy included data on intravenous antibiotics and some of the highly bioavailable oral antibiotics that are sometimes used to treat bacteremia (eg, fluoroquinolones). Only antibiotics that were prescribed within 72 hours after the first blood-culture draw were included, based on the assumption that antibiotics ordered within this timeframe would likely be related to the first blood-culture event. Duration of antibiotic therapy was measured as the average maintenance dose of antibiotics prescribed per day (ie, daily defined dose). To ensure the correctness of data on antibiotic administration and length of stay, a convenience subset of 50 patient admission records were checked manually.

Power calculation

An independent *t* test with a 2-sided $\alpha = .05$, a sample of 305 contaminated episodes in the pre-PCR period and 464 contaminated episodes in the post-PCR period provided 80% power to detect a standardized mean difference of 0.206. G*Power software was used for power analyses.[19]

Statistical analysis

For descriptive statistics, means and standard deviations were calculated for continuous variables, and counts and percentages for categorical variables. The χ^2 test and the 2-sample independent *t* test were used to determine associations between main exposure variable and secondary exposure variables. Variables associated ($P < .10$) with both the outcome variables in crude analyses were assessed further in the multivariable model. Generalized linear models with a negative binomial distribution were used for

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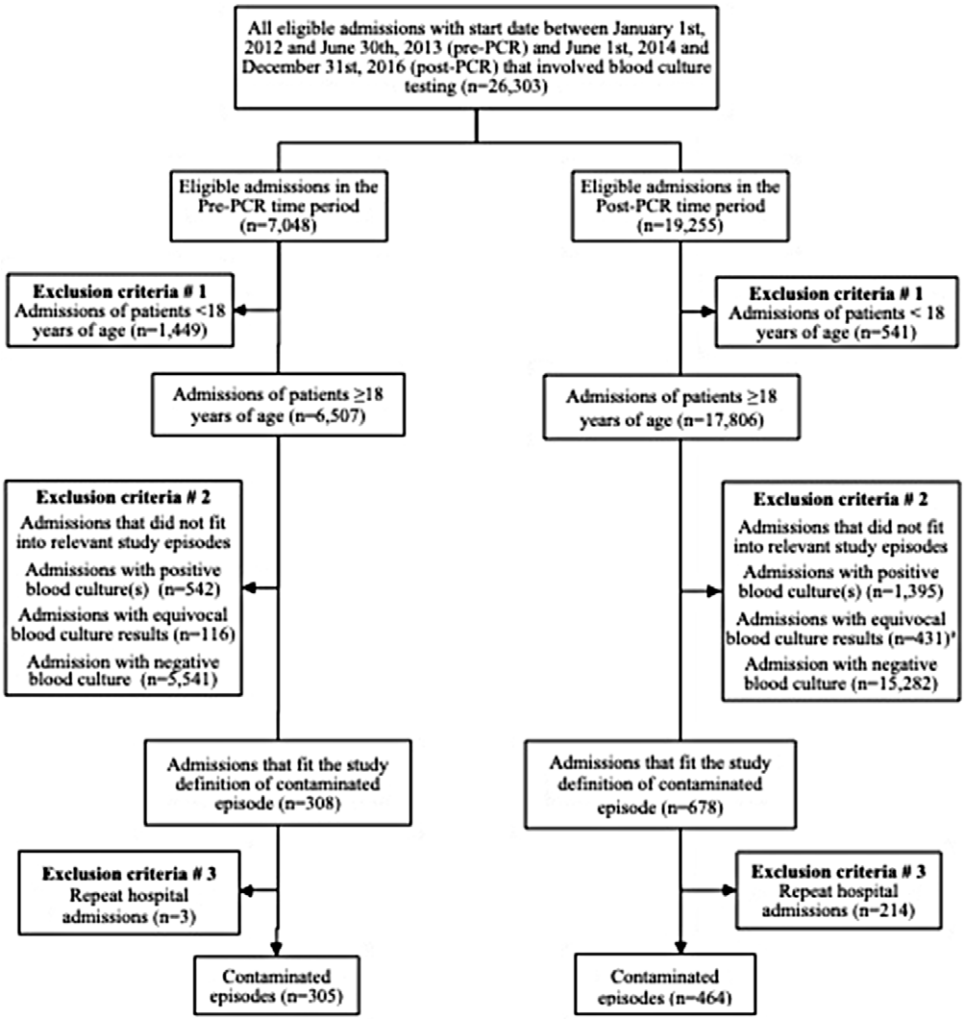

Fig. 1. Flowchart of study participants. [a]Equivocal accounts for any combination of blood culture results that did not strictly fit into positive, negative, or contaminated category.

univariable and multivariable analysis of both outcomes. The final multivariable model was developed by adding secondary exposure variables in a forward stepwise selection process. We used the Akaike information criterion (AIC) value to assess model fit.

A segmented regression analysis was performed to ascertain trends before and after the introduction of the PCR-based BCID system. Thus, we tested the primary exposure variable (PCR status), a time variable (in months) and a 2-way interaction term between the time variable and primary exposure variable against the outcome. If any significant associations were detected during segmented regression analysis ($P < .05$), the same model would be used to create the final multivariable model by adding relevant covariates in a forward stepwise selection process. The model fit for the multivariable model would be based on the smallest AIC. Segmented regression analysis allowed for comparison of any difference in outcomes while controlling for the overall trend during the pre-PCR period that could carry over into the post-PCR period. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

In total, 26,303 admissions that included blood-culture testing were identified between January 1, 2012, and June 30, 2013 (pre-PCR group; n = 7,048) and between June 1, 2014, and December 31, 2016 (post-PCR group; n = 19,255). After exclusions, 769 patients with 305 contaminated episodes from the pre-PCR period and 464 contaminated episodes from the post-PCR period were included in the final analytical sample (Fig. 1). Some data (<1%) pertaining to race, marital status, and health insurance were missing. BMI data were missing for up to 5% of patients. Nearly 8% of data were missing information on smoking status, and ~50% of the data were missing on alcohol status.

A comparison of clinical and sociodemographic characteristics between the 2 groups is presented in Table 1. Although we were able to obtain data on underlying diseases relevant to the study outcomes, the numbers in each group were not sufficient for multivariable analysis.

Trend over time

The segmented regression analysis did not reveal an effect of time on the association between primary exposure (PCR status) and either study outcome, that is, length of hospital stay (Fig. 2) and days of antibiotic therapy (Fig. 3). The 2-way interaction term between the time variable and primary exposure was not significant for both outcomes ($P \geq .05$) and therefore were not included in the final multivariable models.

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Table 1. Clinical and Sociodemographic Characteristics of Study Participants by PCR Status

Characteristic	Before PCR (n = 305) No. (%)	After PCR (n = 464) No. (%)	*P* Value[a]
Age group			.751
<50 y	80 (26.2)	108 (23.3)	
50–61 y	76 (24.9)	128 (27.6)	
62–73 y	75 (24.6)	112 (24.1)	
>73 y	74 (24.3)	116 (25.0)	
Sex			.586
Male	149 (48.9)	236 (50.9)	
Female	156 (51.1)	228 (49.1)	
Race[b]			.658
Black	45 (14.8)	61 (13.2)	
White	240 (78.9)	376 (81.6)	
Other[c]	19 (6.3)	24 (5.2)	
Alcohol status[d]			.543
Drinks alcohol[e]	49 (24.0)	88 (26.5)	
Does not drink alcohol	155 (76.0)	244 (73.5)	
Smoking status[f]			.123
Smoker[g]	167 (58.8)	273 (64.5)	
Nonsmoker	117 (41.2)	150 (35.5)	
Health insurance[b]			.008
Yes	278 (97.2)	429 (92.7)	
No	8 (2.8)	34 (7.3)	
Body mass index (BMI)[h]			.217[i]
Mean (SD)	29.7 (9.4)	30.6 (10.1)	
Admission from ED			.208
Yes	193 (63.3)	314 (67.7)	
No	112 (36.7)	150 (32.3)	
ICU stay			.697
Yes	112 (36.7)	164 (35.3)	
No	193 (63.3)	300 (64.7)	
Underlying disease			
Chronic obstructive pulmonary disease			<.001[j]
Yes	2 (0.7)	47 (10.1)	
No	303 (99.3)	417 (89.9)	
Chronic kidney disease			1[j]
Yes	0 (0.0)	1 (0.2)	
No	305 (100.0)	463 (99.8)	
Liver cirrhosis			.156[j]
Yes	0 (0.0)	4 (0.9)	
No	305 (100.0)	460 (99.1)	
Diabetes mellitus			.460
Yes	34 (11.1)	60 (12.9)	
No	281 (88.9)	404 (87.1)	

Note: ED, emergency department; ICU, intensive care unit; SD, standard deviation.
[a]χ^2 test.
[b]<1% missing data.
[c]Other includes Asian, Hawaiin, Pacific Islander, Native American.
[d]<50% missing data.
[e]Drinks alcohol includes drinks alcohol daily, drinks alcohol every other day, drinks alcohol occasionally.
[f]≤8% missing data.
[g]Smoker includes current smoker, former smoker, daily smoker.
[h]<5% missing data.
[i]2-sample independent *t* test.
[j]Fisher exact test.

Duration of hospital stay

Rapid PCR-based blood-culture testing was not associated with a significant change in the length of hospital stay (LOS) for patients with contaminated blood cultures ($P = .413$) (Table 2). The mean adjusted LOSs for patients with contaminated blood cultures before and after the implementation of the rapid identification system were 10.8 days (95% confidence interval [CI], 9.8–11.9) and 11.2 days (95% CI, 10.2–12.3), respectively. A comparison of the unadjusted and adjusted mean length of stay is presented in Table 3.

Days of antibiotic therapy

Similar to LOS, duration of antibiotic therapy for patients with contaminated blood culture before and after implementation of rapid PCR blood culture testing did not differ significantly ($P = .543$) (Table 4). In the pre-PCR period, patients were treated with antibiotics for an average of 5.1 days (95% CI, 4.5–5.7), and during the post-PCR period patients were treated for 5.3 days (95% CI, 4.8–5.9), after controlling for ICU stay during hospitalization. A comparison of the unadjusted and adjusted mean days of antibiotic therapy is presented in Table 3.

Discussion

Results of this study indicate that the use of a molecular-based rapid blood culture identification system did not affect clinical outcomes in patients with contaminated cultures. Similarly, past studies on contaminated blood culture have also largely shown an insignificant impact of PCR testing on clinical outcomes.[16,18,20] Several reasons may explain the lack of impact of PCR testing on clinical outcomes associated with blood-culture contamination.

First, clinicians continue to fear undertreating or missing real infections and are thus quick to respond to any positive blood culture. For example, although rare, given the serious consequences of untreated infection due to usual contaminants, such as coagulase-negative staphylococci, previous studies have shown

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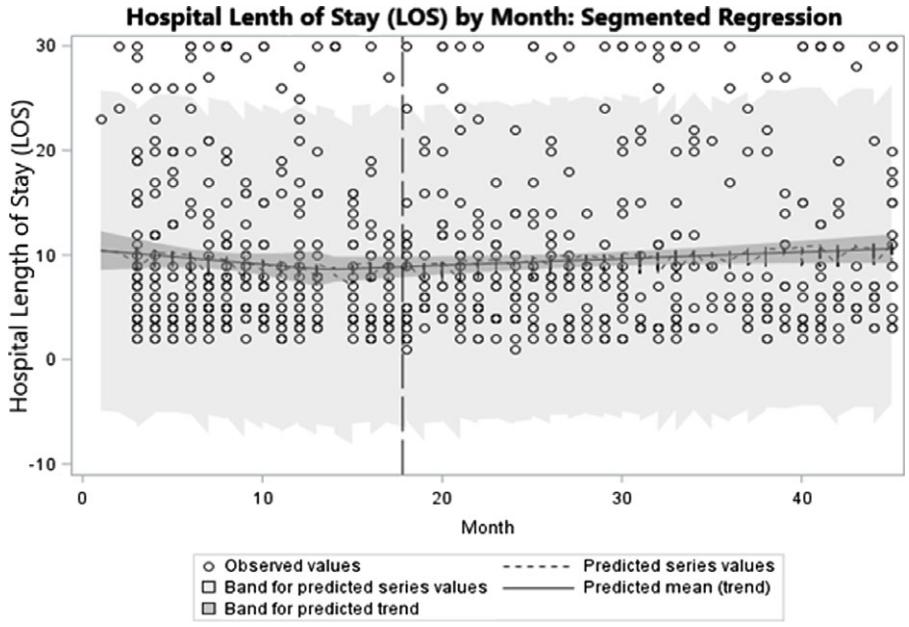

Fig. 2. Segmented regression analysis of length of hospital stay (LOS) versus time. The vertical line designates the introduction of the rapid blood-culture system (BCID). The open circles are LOS for individual patients. The predicted series values (dashed line) vary in a very close proximity to the predicted mean trend (solid line). The (narrow) band for the predicted mean trend is at the 95% confidence level, whereas the (wider) band is for 95% likelihood prediction band of individual series values. At introduction of BCID (vertical line), neither significant vertical change (jump or drop) in mean trend line, nor statistically significant change of mean trend (slope) for LOS was observed.

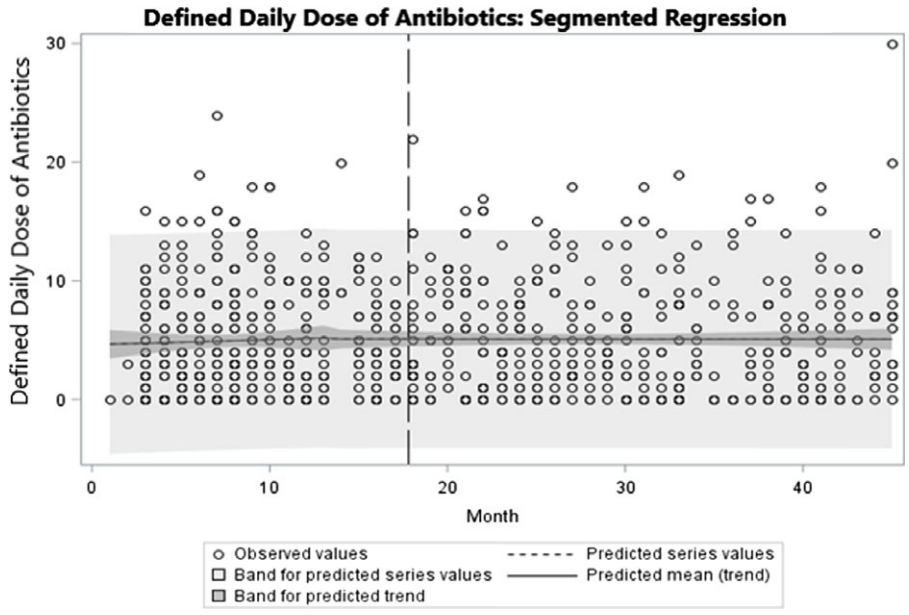

Fig. 3. Segmented regression analysis for defined daily dose of antibiotic therapy (DDD) versus time. The vertical line designates the introduction of the rapid blood-culture system (BCID). The open circles are days of antibiotic therapy for individual patients. The predicted series values (dashed line) and the predicted mean trend (solid line) are almost undistinguishable. The (narrow) band for the predicted mean trend is at the 95% confidence level, whereas the (wider) band is for 95% likelihood prediction band of individual series values. At introduction of BCID (vertical line), neither significant vertical change (jump or drop) in mean trend line, nor statistically significant change of mean trend (slope) for DDD was observed.

that clinicians lean toward management of patients with contaminated blood cultures similar to true infections.[21,22] Second, many clinicians do not fully appreciate harms associated with inappropriate treatment of blood-culture contamination such as prolongation of hospital stay, excess costs, emergence of antibiotic resistance, or *Clostridiodes difficile* infection.[23–25] Increased awareness and education among clinicians is needed regarding the negative impact of contaminated blood cultures.

To be most effective, rapid PCR-based BCID systems should be coupled with an antimicrobial stewardship program (ASP) that can assist clinicians with real-time interpretation and appropriate clinical response. At our institution, the introduction of the BCID system was accompanied by a passive educational program. Past studies have shown that a robust ASP, that monitors patient management and provides feedback in real time, utilized in combination with rapid PCR testing, significantly reduces unwanted clinical consequences in patients with true bloodstream infections.[17,20,26] The influence of a strong ASP on patient outcomes has also been demonstrated in conjunction with conventional blood-culture methods.[20] However, to obtain maximum benefit, the implementation of new technology should be accompanied by decision support tools and interpretive guidance.[22] At the Nebraska Medical Center, the ASP has developed recommendations and an educational program to guide antimicrobial use based on the BCID results.[27]

A strength of our study was the larger sample size of patients with contaminated blood cultures in both pre-PCR and post-PCR groups than in previous studies, which allowed greater precision around the estimates. An advantage of the segmented regression analysis is that it allows and accounts for unintended consequences of interventions and policy changes that might have had an impact on study outcomes.

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Table 2. Final Multivariable Model for Length of Stay (LOS) After Adjustment of Covariates

Covariates	Adjusted Mean LOS Ratio (95% CI)[a] (n = 769)	*P* Value
PCR status		.413
Before PCR	1	
After PCR	1.04 (0.95–1.14)	
Age group		.016
<50 y	1	
50–61 y	1.13 (0.99–1.29)	
62–73 y	1.18 (1.03–1.35)	
>73 y	0.98 (0.85–1.13)	
Race		.065
Black	1	
White	0.99 (0.87–1.15)	
Other[b]	1.26 (1.00–1.59)	
Admission from ED		<.001
No	1	
Yes	0.65 (0.59–0.72)	
ICU stay		<.001
No	1	
Yes	1.83 (1.66–2.01)	

Note. CI, confidence interval; ED, emergency department; ICU, intensive care unit.
[a]Adjusted for age, race, admission from ED, ICU stay.
[b]Other includes Asian, Hawaiian, Pacific Islander, Native American.

Table 3. Comparison of Adjusted and Unadjusted Means for Each Outcome.

	Unadjusted Mean (95% CI) (n = 769)			Adjusted Mean (95% CI) [a,b] (n = 769)		
Clinical Outcomes	Pre-PCR (n = 305)	Post-PCR (n = 464)	*P* Value	Pre-PCR (n = 305)	Post-PCR (n = 464)	*P* Value
Days of hospital stay	9.5 (8.7–10.3)	9.5 (8.9–10.2)	.888	10.8 (9.8–11.9)	11.2 (10.2–12.3)	.413
Days of antibiotic therapy	4.9 (4.4–5.6)	5.1 (4.6–5.6)	.680	5.1 (4.5–5.7)	5.3 (4.8–5.9)	.543

Note. CI, confidence interval; PCR, polymerase chain reaction; LOS, length of stay; ED, emergency department; ICU, intensive care unit.
[a]Mean LOS adjusted for trend over time, age, race, admission from ED and ICU stay during hospitalization.
[b]Mean days of antibiotic therapy adjusted for trend over time and ICU stay during hospitalization.

This study had several limitations. Potential information and misclassification bias is inherent in the retrospective study design. We noted differences between the groups regarding the presence of chronic obstructive pulmonary disease (COPD) and health insurance status, which could indicate cohort mismatch. Additionally, we did not have sufficient data to control for some underlying diseases, which might have resulted in confounding. Additional confounders were ASP efforts, clinician behavior, and staff turnover. The institution where this study was conducted is an academic medical center and thus has many trainees who turnover on a regular basis. As noted, the organization has in place a robust ASP, and various efforts were ongoing to improve antimicrobial use during the study period. Finally, we did not assess whether patients had indwelling prosthetic devices (eg, prosthetic heart valves, vascular grafts, etc), which could influence the clinical assessment of blood culture contamination.

Table 4. Final Multivariable Model for Antibiotic Days of Therapy (Abx DOT) After Adjustment of Covariates

Covariates	Adjusted mean Abx DOT ratio (95% CI)[a] (n = 769)	*P* Value
PCR status		.543
Pre-PCR	1	
Post-PCR	1.05 (0.90–1.21)	
ICU stay		<.001
No	1	
Yes	1.54 (1.32–1.79)	

Note. Abx DOT, days of antibiotic therapy; CI, confidence interval; PCR, polymerase chain reaction assay; ED, emergency department; ICU, intensive care unit.
[a]Adjusted for ICU stay during admission.

In conclusion, the introduction of a rapid PCR-based blood culture identification system did not improve clinical outcomes, such as length of hospital stay and duration of antibiotic therapy, in patients with contaminated blood cultures.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2022.314

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