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BRIEF REPORT

Impact of Rapid Identification and Stewardship Intervention on Coagulase-Negative *Staphylococcus* Bloodstream Infection

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We investigated the impact of rapid diagnostic testing with and without algorithm-based stewardship recommendations on antibiotic use for bloodstream infection with coagulase-negative staphylococci. A significant reduction in antibiotic days of therapy was achieved in the stewardship intervention group that was not seen with rapid diagnostic testing alone.

Keywords. blood culture; coagulase-negative; rapid diagnostics; *Staphylococcus*; stewardship.

Coagulase-negative staphylococci (CoNS) are the most common organisms isolated from blood cultures. CoNS-positive blood cultures often represent contamination even when growth is detected in multiple blood culture sets [1]. In rare circumstances, CoNS are a true cause of bloodstream infections (BSI) [2, 3]. Differentiating CoNS BSI from blood culture contamination is a major challenge that leads to unnecessary consumption of healthcare resources, including antibiotics, laboratory tests, and diagnostic procedures [4]. Antibiotics are often continued for several days while awaiting further diagnostic tests, resulting in an increased likelihood for adverse events and/or antibiotic resistance. In a case-control study, patients with contaminated blood cultures remained in the hospital for a median 5 days longer than matched control patients with negative blood cultures, resulting in higher total healthcare costs [5]. Antibiotic therapy, laboratory testing, and effort from hospital personnel alone account for >30% of costs attributable to blood culture contamination [6].

Excessive healthcare utilization following CoNS-positive blood cultures can be partially attributed to variability in patient management. A recent randomized trial compared algorithm-based and provider-directed therapy for staphylococcal bacteremia. CoNS bacteremia cases were categorized as simple, uncomplicated, or complicated based on standardized clinical and microbiological criteria [7]. The investigators found that patients assigned to algorithm-based treatment had similar clinical outcomes as those assigned to provider-directed treatment; however, surprisingly, treatment durations among patients with CoNS bacteremia did not vary between groups [7]. This may be due to the fact that rapid molecular diagnostic tests (RDTs) from positive blood cultures were not employed and patients received up to 3 days of empiric antibiotics prior to study enrollment. To address these points, we designed a quasi-experimental study to determine the impact of RDTs with and without algorithm-based management of CoNS bacteremia. We hypothesized that rapid identification and early stewardship intervention with an algorithm-based approach would be safe and effective, and result in lower rates of antibiotic use with improved healthcare resource utilization.

METHODS

Consecutive patients with blood cultures positive for *Staphylococcus* species (other than *S aureus* and *S lugdunensis*) were included across 3 independent 4-month time periods. The pre-RDT time period was in 2019–2020, followed by a post-RDT, prealgorithm period in 2020–2021 and a prospective post-RDT, postalgorithm period in 2021–2022. During the pre-RDT period, CoNS were identified by matrix-assisted laser desorption/ionization–time of flight (Bruker, Billerica, Massachusetts) the day after blood culture positivity. Antibiotic susceptibility testing was performed with Microscan WalkAway (Beckman Coulter, Brea, California) within 72 hours. In 2020, GenMark Dx (a member of the Roche group) was introduced and provided CoNS identification within 2 hours of Gram stain results; RDT results were reported directly to the stewardship team between 06:00 and 22:00 daily. Patients were excluded if they were already being treated for a separate gram-positive BSI at the time of CoNS identification, had polymicrobial bacteremia, died within 48 hours of blood culture collection, or were diagnosed with coronavirus disease 2019 (COVID-19) prior to CoNS bacteremia. During the prospective post-RDT, postalgorithm period, standardized criteria were employed to categorize CoNS BSI cases

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as simple, uncomplicated, or complicated (Supplementary Figure). Within each category, standardized recommendations for antibiotics, blood cultures, and monitoring were provided (Supplementary Table). Our stewardship team classified cases, intervened in real time, and recorded results in an electronic database. Standardized study definitions were applied retrospectively to patients in the prealgorithm time periods. All cases were adjudicated by study investigators to ensure consistency across study periods. The primary outcome was total antibiotic days of therapy (DOT), defined as any day targeted antibiotics were administered, for patients with simple CoNS bacteremia. Our secondary objective was to confirm the safety of this approach measured by all-cause mortality, 30-day hospital readmissions, and recurrent CoNS BSIs. The study was approved by the University of Pittsburgh institutional review board with waiver of informed consent.

Continuous and categorical variables were compared by Mann-Whitney U and χ^2 tests, respectively. A P value of <.05 (2-tailed) was considered statistically significant. All analyses were conducted with GraphPad Prism version 9.4.0 software (San Diego, California).

RESULTS

Three hundred and seven patients with CoNS bacteremia were identified during the study periods. Forty-seven were excluded for polymicrobial cultures, 36 for COVID-19, 18 were transferred from an oustide hospital, 15 for early death or comfort-directed care, and 9 patients had >1 reason for exclusion. The remaining 182 were included from pre-RDT (n = 65), post-RDT, prealgorithm (n = 60), and postalgorithm (n = 57) time periods. The median age was 62 (range, 17–97) years, 54% (98/182) were male, and the median Charlson Comorbidity Index (CCI) score was 5 (0–15). Patients in the post-RDT, postalgorithm group had a higher median age and CCI than those in the other time periods (Table 1). Forty-two percent (76/182) of patients had a central venous catheter at the time of bacteremia and 8% (15/182) of patients had a history of solid organ transplant. There were no other differences in patient demographics across cohorts.

Overall, 69% (125/182), 19% (35/182), and 12% (22/182) of cases were classified as simple, uncomplicated, or complicated bacteremia, respectively. Seven cases, initially classified as simple bacteremia prospectively, were subsequently reclassified as uncomplicated or complicated after investigator adjudication.

Significant reductions in antibiotic DOT were observed in the post-RDT, postalgorithm period, but not in the post-RDT, prealgorithm period (Table 1). Median DOT did not vary significantly for patients with simple, uncomplicated, or complicated bacteremia between the pre-RDT and post-RDT, prealgorithm periods. In contrast, median DOT were reduced to 0 ($P = .003$) for simple BSI in the post-RDT, postalgorithm period. Fifty-four percent (31/57) of patients received antibiotics for <24 hours in the post-RDT, postalgorithm period compared to 33% ($P = .006$) in the combined prealgorithm periods. Ninety-five percent (140/147) of patients who received antibiotics were treated with vancomycin; reductions in vancomycin DOT were consistent with overall DOT (Table 1). Antibiotics were avoided entirely in 28% of CoNS cases in the postalgorithm period compared to 15% of cases in the prealgorithm periods ($P = .04$). The overall 30-day, all-cause mortality rate was 14.2% (26/182) and did not vary across cohorts. Rates of recurrent BSI and 30-day readmission were also similar across cohorts. The median length of stay was numerically (7 vs 10 days), but not statistically lower in the postalgorithm period ($P = .10$).

DISCUSSION

Management of CoNS BSI represents a major challenge in diagnostic stewardship that is associated with significant antibiotic use and healthcare costs. In the current study we have shown that RDTs play an important role in reducing antibiotic DOT, but only when combined with an early, algorithm-directed stewardship intervention. Our innovative approach to management of CoNS bacteremia corroborates findings from prior algorithm-based interventions for staphylococcal BSI [7]; however, we have extended these findings to show the additional impact on patient outcomes by incorporating RDT for CoNS—the most common organisms identified in positive blood cultures. By developing criteria that could easily be applied by our stewardship team within hours of a positive blood culture result, we were able to standardize management of CoNS bacteremia. Combined RDT plus algorithm-directed management resulted in a significant reduction in unnecessary antibiotic prescribing and notable trends toward shorter durations of hospitalization. These data have major implications considering that even with robust stewardship efforts and targeted communication, nearly 87% of patients with contaminated blood cultures receive antibiotics for an average of 7 days and stay in the hospital for a median duration of 7 days [8]. Thus, pairing RDT with early algorithm-based management can significantly reduce healthcare resource utilization.

A key finding from our analysis was a reduction in unnecessary vancomycin use. In fact, our team intervened prior to the first dose of antibiotic therapy in 28% of patients during our prospective intervention period. This is in comparison to just 15% of patients managed in earlier cohorts. Moreover, we reduced the median duration of vancomycin therapy to <1 DOT for patients with simple BSI (Table 1), which compares favorably to a vancomycin DOT range of 3.5–6.5 in prior studies of contaminated blood cultures [4, 9, 10]. Although our study was not powered to detect differences in rates of vancomycin-induced acute kidney injury (AKI), we anticipate that our approach would show further benefits when tested

Table 1. Patient Demographics, Clinical Characteristics, and Outcomes of Patients With Coagulase-Negative *Staphylococcus* Bacteremia, Stratified by Study Period

Characteristic	All Patients (N = 182)	Pre-RDT, Prealgorithm (n = 65)	Post-RDT, Prealgorithm (n = 60)	Post-RDT, Postalgorithm (n = 57)	*P* Value[a]
Patient demographics					
Male sex	98 (54)	35 (54)	34 (57)	29 (51)	.59
Median age, y (range)	62 (17–97)	57 (17–89)	61 (18–97)	65 (23–86)	.05
SOT	15 (8.2)	4 (6.2)	5 (8.3)	6 (10.5)	.45
PWID	5 (2.7)	1 (1.6)	2 (3.3)	2 (3.5)	.67
CCI, median (range)	5 (0–15)	4 (0–11)	4 (0–11)	5 (0–15)	.02
Bacteremia characteristics					
Staphylococcus epidermidis	140 (77)	55 (85)	41 (68)	44 (77)	.95
BSI classification					
Simple	125 (69)	46 (71)	40 (67)	39 (68)	.96
Uncomplicated	35 (19)	10 (15)	15 (25)	10 (18)	.13
Complicated	22 (12)	9 (14)	5 (8.3)	8 (14)	.59
Single bottle positive	125 (69)	41 (63)	41 (68)	43 (75)	.22
Simple	105 (84)	35 (76)	36 (90)	34 (87)	.60
Uncomplicated	9 (26)	1 (10)	4 (27)	4 (40)	.39
Complicated	11 (50)	5 (56)	1 (20)	5 (63)	.66
Outcomes					
Empiric therapy avoided	35 (19)	8 (12)	11 (18)	16 (28)	.04
<24 h of therapy	71 (39)	20 (31)	21 (35)	31 (54)	.006
Median days of therapy (range)[b]					
Simple	1.0 (0–22.3)	1.2 (0–15.0)	1.2 (0–22.3)	0 (0–12.9)	.003
Uncomplicated	5.3 (0–20.2)	10.8 (0–17.5)	3.5 (0–20.2)	4.8 (0–15.3)	.53
Complicated	18.3 (2.1–58.7)	9.5 (2.1–36.3)	21.7 (15–58.7)	23.5 (7.2–43.3)	.37
Median days of vancomycin (range)					
Simple	0.5 (0–18.1)	1.2 (0–15.7)	0.3 (0–18.1)	0 (0–12.9)	.02
Uncomplicated	3.5 (0–17.5)	3.7 (0–17.5)	2.6 (0–13.1)	4.8 (0–13.1)	.50
Complicated	4.7 (0–44.9)	4.3 (0–36.3)	8.8 (0.4–44.9)	1.0 (0–43.3)	.91
Recurrent BSI[c]	4 (2.5)	3 (4.9)	1 (1.9)	0 (0)	.19
30-d readmission[c]	33 (21)	15 (25)	10 (20)	8 (17)	.49
30-d mortality or hospice	26 (14.2)	7 (11)	9 (15)	10 (17)	.40
Infectious disease consultation	96 (53)	36 (55)	33 (55)	27 (47)	.33
Pharmacokinetics consultation	…	…	42 (70)	44 (77)	.38
AKI attributed to vancomycin[d]	12 (6.6)	5 (7.7)	4 (6.7)	3 (5.3)	.63
Median LOS after positive blood culture (range)[c]	10 (2–405)	10 (2–405)	10.5 (3–93)	7 (2–51)	.10

Data are presented as No. (%) unless otherwise indicated. Each 4-month time period was separated by an 8-month washout that allowed for the same months to be evaluated in each phase of the study. Given that no significant differences were identified in the prealgorithm time periods, they were combined and compared to the postalgorithm time period for analysis.

Abbreviations: AKI, acute kidney injury; BSI, bloodstream infection; CCI, Charlson Comorbidity Index; LOS, length of stay; PWID, person who injects drugs; RDT, rapid diagnostic test; SOT, solid organ transplant.

[a] *P* values highlight the statistical significance of both prealgorithm periods compared to the postalgorithm period.

[b] Ninety-five percent of patients treated empirically received vancomycin.

[c] Patients who died during index hospitalization were excluded from 30-day readmissions and length of stay calculations.

[d] Includes patients who developed AKI by the Kidney Disease–Improving Global Outcomes criteria after receiving vancomycin for ≥48 hours.

across larger patient populations. Reducing antibiotic DOT and limiting the collection of repeat blood cultures will likely decrease durations of hospitalization. After controlling for age, race, body mass index, and sepsis, prior investigations have found that blood culture contamination is associated with an increased length of stay, higher rates of AKI, and more frequent echocardiographs when compared to patients with negative blood cultures [4].

Previous studies have not demonstrated reductions in vancomycin DOT, time to vancomycin discontinuation, or hospital length of stay after implementation of RDT alone [11]. These findings were despite stewardship recommendations being provided to the primary team at the time of the Gram stain or RDT results. These findings mirror our experience before and after RDTs were implemented. Significant improvements did not occur until we implemented a standard management protocol for CoNS. Another key difference between our study and previous reports is the RDT platform that was employed. Herein, we studied the GenMark Dx, which identifies several CoNS targets enabling our team to quickly assess and classify patients. Variation in types of RDTs highlights that stewardship teams should adopt approaches tailored to the molecular tools available at their facility.

Overall, we did not identify an increase in recurrent BSI, hospital readmissions, or mortality among patients in our intervention cohort. These data support the safety of our approach and should give providers reassurance in rapidly de-escalating antibiotics in the setting of simple CoNS bacteremia. Our findings are consistent with prior quasi-experimental studies [9, 11] and supported by a pragmatic randomized controlled clinical trial [7].

Finally, we acknowledge some limitations of this pilot study. First, our initial pre-RDT time period was before the onset of the COVID-19 pandemic. While patients with COVID-19 were excluded, it is possible that changes within the healthcare environment, including blood culture collection practices, may have influenced our findings. Second, our study was not powered to detect differences in clinical outcomes such as patient mortality, rates of AKI, and hospital length of stay, and thus, the impact of RDT plus algorithm-based interventions for patients with CoNS BSI should be confirmed by larger multicenter studies. Finally, our approach was aided by a robust stewardship team that was able to intervene in real time. It is unclear if our findings can be reproduced in settings without significant stewardship resources. Nonetheless, we have demonstrated that a combined RDT and early, algorithm-directed stewardship intervention effectively reduced antibiotic DOT for CoNS bacteremia without any increase in recurrent infection or hospital readmissions. We view our findings as a benchmark for future studies to assess additional benefits to this approach.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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