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# A Stewardship Approach To Optimize Antimicrobial Therapy through Use of a Rapid Microarray Assay on Blood Cultures Positive for Gram-Negative Bacteria

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**A Gram-negative (GN) blood culture microarray assay with an antimicrobial stewardship program (ASP) intervention was evaluated in 126 patients with GN bacteremia. The median time to optimal therapy was shorter in the postintervention group than in the preintervention group (49.3 h versus 38.5 h, respectively; $P = 0.0199$). ASP can utilize microarray technology to decrease the time to optimal antimicrobial therapy.**

The treatment of Gram-negative bloodstream infections (GN-BSI) is particularly complicated due to high rates of resistance from multiple resistance mechanisms, including the production of extended-spectrum β-lactamase (ESBL) and carbapenemase enzymes, leaving limited treatment options (1, 2). Molecular diagnostic assays can produce results faster than traditional identification and susceptibility testing methods and may help decrease the time to appropriate antimicrobial therapy (3–18). The Verigene Gram-negative blood culture (BC-GN) assay (Nanosphere, Inc., Northbrook, IL) is a qualitative *in vitro* diagnostic test for the rapid detection and identification of select Gram-negative bacteria and resistance markers (17). The purpose of this study was to evaluate the impact of an antimicrobial stewardship program (ASP) on the time to optimal antimicrobial therapy, utilizing rapid organism and resistance identification via the BC-GN test, on patients with GN-BSI.

This was a retrospective, quasiexperimental, and preintervention/postintervention study conducted at University of Florida Health and was approved by the University of Florida Health Science Center Jacksonville institutional review board. All inpatient adults with documented GN-BSI between 15 September 2013 and 15 February 2014 (pre-BC-GN period) and between 15 September 2014 and 15 February 2015 (post-BC-GN period) were evaluated for inclusion. Exclusion criteria included polymicrobial BSI, documented infections caused by organisms not identified by the BC-GN test, incarcerated patients, involvement with other investigational protocols, or death prior to culture results. During the pre-BC-GN period, the ASP reviewed the prescribed antimicrobial agents and provided pharmacotherapeutic recommendations to prescribers as microbiology information became available during normal business hours. In the postintervention period, the BC-GN test was performed according to the manufacturer's specifications (17), and the results were reported in a similar fashion as done previously (10). Microbiology paged the ASP 24 h per day, 7 days per week with BC-GN test results. The ASP contacted physicians during normal business hours with pharmacotherapeutic recommendations based on BC-GN test results. All BC-GN test results were confirmed by conventional microbiological methods, including rapid spot tests (oxidase and indole) and the Vitek 2 GN identification and GN-73 susceptibility cards (bioMérieux, Durham, NC).

After retrospective identification of patients with GN-BSI, the electronic health record (EHR) was used to identify patients for inclusion and exclusion criteria and the time, in hours, from blood culture collection to the administration of optimal and effective antimicrobial therapy. The time to optimal and effective antimicrobial therapy was defined similarly to that in other published work (8). Data collected from the EHR included demographics, microbiology results, antimicrobials administered, hospital course, and hospital charges. The coinvestigators independently validated all primary outcomes.

During statistical analysis, continuous variables were summarized using means ± standard deviations and analyzed using Wilcoxon's rank sum test. Categorical variables were summarized using counts and percentages and analyzed using Fisher's exact test. The differences in the time to effective therapy, length of stay (LOS), and infection-related LOS between groups were compared using Wilcoxon's rank sum test. The time to optimal therapy, stratified by group, was analyzed to test for homogeneity across strata. Using preliminary data from previous studies, an expected difference of 1.0 days and a standard deviation of 1.75 days were assumed (10). For a two-sided two-independent-sample *t* test with a 5% significance level to have 80% power to detect this expected difference, a sample size of 100 total patients, with 50 per group, was required. All analyses were performed using SAS version 9.4 for Windows.

During the study period, 203 patients were identified and screened for study inclusion, and 126 met the criteria. The primary reason for exclusion was polymicrobial BSI ($n = 50$). The

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**TABLE 1** Comparison of baseline characteristics for the pre- and postintervention BC-GN groups

| Characteristic[a] | Preintervention group ($n = 59$) | Postintervention group ($n = 67$) | *P* value |
|---|---|---|---|
| Age (median) (yr) | 58 | 58 | 0.7192 |
| Male sex (no. [%]) | 31 (52) | 33 (49) | 0.7249 |
| Charlson comorbidity index (median) | 2 | 2 | 0.4247 |
| Pitt bacteremia score (median) | 2 | 3 | 0.1836 |
| ID consult (no. [%]) | 17 (29) | 15 (22) | 0.4209 |
| Service (no. [%]) | | | |
| Hospitalist | 19 (32) | 19 (28) | 0.1478 |
| Non-ICU teaching | 27 (46) | 21 (31) | |
| MICU | 8 (14) | 19 (28) | |
| SICU | 5 (9) | 8 (12) | |
| Organism (no. [%]) | | | |
| *Acinetobacter* spp. | 2 (3) | 3 (4) | 0.9125 |
| *Enterobacter* spp. | 6 (10) | 8 (12) | |
| *E. coli* | 26 (44) | 29 (43) | |
| *Klebsiella oxytoca* | 1 (2) | 2 (3) | |
| *K. pneumoniae* | 15 (25) | 12 (18) | |
| *Proteus* spp. | 4 (7) | 8 (12) | |
| *Pseudomonas aeruginosa* | 5 (8) | 5 (7) | |
| Source (no. [%]) | | | |
| Endovascular | 14 (24) | 9 (13) | 0.6211 |
| Intra-abdominal | 5 (9) | 10 (15) | |
| Genitourinary | 29 (49) | 30 (45) | |
| Respiratory | 5 (9) | 8 (12) | |
| SSTI | 2 (3) | 5 (7) | |
| Other | 1 (2) | 1 (2) | |
| Unknown | 3 (5) | 4 (6) | |

[a] ICU, intensive care unit; MICU, medical ICU; SICU, surgical ICU; SSTI, skin and soft tissue infection.

**TABLE 2** Indications for therapeutic optimization by treatment group[a]

| Reason (no. [%]) | Preintervention group ($n = 59$) | Postintervention group ($n = 67$) |
|---|---|---|
| Continued on broad-spectrum therapy | 3 (5) | 2 (3) |
| Deescalation of Gram-positive antibiotic | 7 (12) | 6 (9) |
| Deescalation of primary Gram-negative antibiotic | 25 (42) | 34 (51) |
| Deescalation of secondary Gram-negative antibiotic | 4 (7) | 3 (5) |
| Escalation to appropriate therapy | 12 (20) | 7 (10) |
| Initiated on optimal therapy | 6 (10) | 13 (19) |
| Never reached optimal therapy | 2 (3) | 2 (3) |

[a] $P = 0.5079$.

baseline characteristics and identified organisms were similar between groups (Table 1). ESBL- and carbapenemase-producing pathogens were identified in 8 patients in the pre-BC-GN group and 4 patients in the post-BC-GN group. The median time to optimal therapy was shorter in the postintervention group 49.3 h [95% confidence interval {CI}, 41.7, 65.0] than in the preintervention group 38.5 h [95% CI, 28.0, 45.6]; $P = 0.0199$). The indications for therapeutic optimization per treatment group (Table 2) and the secondary outcomes (Table 3) were similar between groups.

There was 100% agreement between all BC-GN identification results and conventional methods. The BC-GN test detected the resistance markers for CTX-M ($bla_{\text{CTX-M}}$) in three clinical isolates (2 *Escherichia coli* and 1 *Proteus mirabilis*) and 1 *Klebsiella pneumoniae* carbapenemase (KPC) ($bla_{\text{KPC}}$) in a *K. pneumoniae* isolate. All resistance markers identified on the BC-GN test displayed phenotypic resistance on conventional susceptibility testing. There were no ESBL- or carbapenemase-producing isolates identified in the postintervention cohort that were not detected by the BC-GN test. The mean time to blood culture positivity was similar between groups (19.4 versus 17.3 h; $P = 0.9649$).

Microarray assays rapidly identify organisms and resistance markers in patients with BSI and have the potential to decrease the time to optimal antimicrobial therapy with ASP intervention. While there is growing literature on the use of rapid diagnostic technology and ASP intervention for Gram-positive BSI (9–12), few studies have evaluated patients with GN-BSI. Bork and colleagues (13) predicted an 18.3-h reduction in the time to optimal therapy and a 3.7-h reduction in the time to effective antimicrobial therapy when utilizing a simulated model based on BC-GN reporting and ASP intervention (13). Similar to this simulation, our study was able to demonstrate a reduction in the time to optimal therapy. With the majority of pathogens in the post-BC-GN group being identified as *E. coli* or *K. pneumoniae*, rapid organism identification allowed the ASP team to recommend the deescalation of Gram-negative antibiotics faster based on the BC-GN result. A majority of the patients in both intervention arms were placed on effective antibiotics shortly after blood culture collection; therefore, the decrease in the time to effective therapy in the postintervention group did not reach statistical significance. While the escalation to appropriate therapy for organisms with identified resistance markers was anticipated to be a major benefit to rapid organism identification, the number of resistant organisms included in the study was small. Because more patients were admitted into intensive care units in the post-BC-GN group, we were not able to show the same reduction in the length of stay and hospital charges seen in previous studies, as some benefit of the intervention may have been masked by a higher level of care required.

There were some limitations to this study. It was conducted at a single institution utilizing a small sample size, with almost a quarter of the screened patients excluded due to polymicrobial BSI, which is a known limitation to some rapid molecular identification tests. The data were retrospectively extracted from the EHR in a nonblinded manner, which allowed for potential information bias. Although differences in baseline demographics between groups were not identified, it is not known whether unmeasured or unreported confounders might have affected the clinical outcome results. A majority of patients had a urinary source of infection, and *E. coli* was the most common pathogen identified. The rates of resistance were relatively low; therefore, institutions with higher rates of resistance with organisms harboring the resistance markers detected by the BC-GN test may have a more profound impact from the intervention. Despite these limitations, a significant time to optimal therapy was achieved.

In conclusion, the BC-GN assay with ASP intervention was able to expedite clinical decision-making and decrease the time to

**TABLE 3** Comparison of secondary outcomes by treatment group

| Outcome | Preintervention group ($n = 59$) | Postintervention group ($n = 67$) | *P* value |
|---|---|---|---|
| Time to effective therapy (median) (h) | 3.6 | 2.9 | 0.7229 |
| Hospital length of stay (mean) (days) | 16.2 | 18.4 | 0.2055 |
| Infection-related length of stay (mean) (days) | 10.3 | 9.5 | 0.9143 |
| 30-day readmission rates (no. [%]) | 10 (18.2) | 9 (14.1) | 0.6195 |
| 30-day mortality (no. [%]) | 4 (7) | 5 (8) | 0.9837 |
| Hospital charges (median) ($) | 58,913 | 97,238 | 0.1093 |
| I-LOS hospital charges (median) ($)[a] | 52,048 | 57,087 | 0.6975 |

[a] I-LOS, infection-related length of stay.

optimal antimicrobial therapy in patients with GN-BSI. Future studies are needed in populations with higher rates of Gram-negative resistance to further elucidate the full impact of this intervention on clinical and economic outcomes.

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