Clinical uptake of antimicrobial stewardship recommendations following Nanosphere Verigene Blood Culture Gram-negative reporting

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We performed a retrospective chart review of patients to determine if the Verigene Gram-negative blood culture (BC-GN) results would lead to earlier deescalation of empiric therapy for inpatients with GN bacteremia with *Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp., and *Escherichia coli* to appropriate targeted coverage. A total of 899 records were reviewed from April 2014 to February 2016 from three institutions within the Baylor Scott & White Health network. The cases were reviewed for initial antibiotic coverage, timing of Verigene results, change in antibiotic coverage, and how these changes related to the timing of Verigene results. The lab reported the BC-GN results and final conventional susceptibility results within 2.5 ± 1.3 and 73.6 ± 40.0 hours from the Gram stain, respectively. Overall, 29.1% of patients were transitioned from empiric to targeted therapy at 12.2 ± 13.5 hours in response to BC-GN results, which was significantly earlier ($P < 0.001$) than results by conventional methods. After accounting for patients already on targeted therapy, polymicrobial infections, and patients deceased or lost to follow-up, we identified antibiotic stewardship opportunities in ~28% of GN infections. Further subanalysis demonstrated site-specific differences in the uptake of stewardship recommendations, whereby 32.4%, 50.5%, and 15.0% of cases at different hospitals demonstrated the expected change in antibiotics. These results suggest that Verigene had the expected impact in a third of the cases and the results reporting algorithm minimized the real-time involvement of the pharmacist while maintaining optimal patient management. However, this impact varied substantially by clinical site and was tempered by variable initial antibiotic coverage and clinician response.

Effective and prompt antimicrobial therapy is crucial for the survival of patients with sepsis (1–3). Rapid molecular technologies aimed at decreasing the time to identification and susceptibility results have recently entered the market (4, 5). The Verigene Gram-Negative Blood Culture (BC-GN) assay is one such rapid panel that detects seven genera, four species, and six resistance markers directly from positive blood cultures (6). We adopted the BC-GN assay in our laboratory to serve the needs of the multisite Baylor Scott and White Health network. For effective implementation, we worked with the Antimicrobial Stewardship Program (ASP) to provide recommended changes to antibiotic therapy based on the species identification and local pathogen susceptibility patterns in the result comments. The goal was to improve patient outcomes by guiding transition of the empiric treatment (vancomycin and piperacillin/tazobactam) to targeted therapy, while simultaneously preventing antibiotic overuse and the development of antibiotic resistance. This study aimed to determine if decreasing the time to blood culture result using the BC-GN system paired with well-defined ASP-recommended therapy changes would impact clinical outcomes. The primary objective was to evaluate the clinical uptake and utilization of the BC-GN results by measuring the reduction in time from positive blood culture to the deescalation of empiric therapy and the switch to the first dose of appropriate antibiotics per the resulting algorithm. As previously published, an algorithm designed using electronic communications and minimum pharmacist intervention was used (7, 8). We also determined if there were any site-specific differences in the uptake of stewardship recommendations within the network.

METHODS

This was a multisite, retrospective chart review of patients admitted with Gram-negative (GN) bacteremia to Baylor University Medical Center, a 1079-bed tertiary referral center in Dallas, Texas, and two smaller acute care hospitals also within the Baylor Scott and White Health network, 574-bed Baylor All Saints and 296-bed Baylor Irving. Blood cultures were performed at the affiliated reference laboratory, med fusion, in Lewisville, Texas. Molecular testing on the positive blood cultures was performed using Verigene BC-GN panel (Nanosphere, Inc., Northbrook, IL). This study was approved by the institutional review board.

Medical records were reviewed from April 2014 to February 2016 from three sites for initial antibiotic coverage, timing of the appearance of Verigene results in the electronic health record (EHR), change in antibiotic therapy (if any), and how these changes compared to the timing of Verigene results. Times were

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documented for blood culture collection, Gram stain, BC-GN result, conventional identification and susceptibilities, and the first dose of appropriate antibiotic. For this study, we chose a subset of GN organisms—*Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp. and *Escherichia coli*—as the recommended change in antibiotics was most different from empiric therapy and was predicted to have a maximum impact upon change in antibiotics in response to stewardship recommendations. Other GN bacteria such as *Pseudomonas aeruginosa*, *Proteus* spp., and *Acinetobacter* spp. were also detected in the assay but were not considered because of the likelihood of minimal impact on empirical antibiotic usage. Appropriate adjustment was defined as deescalation of empiric therapy (vancomycin and piperacillin/tazobactam) to the appropriate targeted coverage such as third- or fourth-generation cephalosporins within 24 hours in response to the stewardship recommendations on the Verigene report *(Table 1)*. Antibiotics were documented based on the date and time that the dose was given as recorded in the EHR. Patients who died during their hospital admission or were discharged before Verigene results were available were excluded.

Blood was collected at individual sites and transported via courier to med fusion. Upon arrival at med fusion, bottles were incubated on the BacT/ALERT automated blood culture system for up to 5 days. When the aerobic or anaerobic bottle was identified as positive for bacterial growth, a Gram stain was performed, with inoculation on appropriate solid agar media. Plates were read after approximately 24 hours of incubation. Identification and susceptibility testing were performed using conventional phenotypic methods, MALDI-TOF and the VITEK®2 (bioMérieux, Durham, NC). The first bottle per bacteremic episode that showed a GN organism on Gram stain was tested using the BC-GN. The BC-GN was also run if the Gram stain showed mixed organisms with Gram-positive or other Gram stain morphologies.

The BC-GN results were called as a critical value to the floor and were released in the EHR. For *Citrobacter* spp. and *Enterobacter* spp., the Verigene report was accompanied by an interpretive comment suggesting the appropriate antimicrobials were fourth-generation cephalosporins and recommending discontinuation of empiric coverage. For *Klebsiella* spp. and *E. coli*, appropriate antimicrobials included third-generation cephalosporins and discontinuation of empiric coverage. The stewardship recommendations were developed by a collaborative team of ASP, infectious disease physicians, and laboratory staff.

Student's *t* test was used to determine statistical significance in cases where intervention was made in response to the rapid Verigene result vs. the availability of the final report based on conventional methods.

Table 1. Targets detected on Verigene Blood Culture Gram-negative panel and associated stewardship comments

Verigene target	Stewardship comments added to the Verigene report
Citrobacter spp., *Enterobacter* spp.	• Consider discontinuing empiric Gram-positive coverage if appropriate. • Consider a fourth-generation cephalosporin if appropriate. • Deescalate further when susceptibility results are available.
Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli	• Consider discontinuing empiric Gram-positive coverage if appropriate. • Consider a third-generation cephalosporin if appropriate. • Deescalate further when susceptibility results are available.
ESBL producer (CTX-M)	• Recommend use of meropenem. • Deescalate when susceptibility results are available.
Carbapenemase producer (KPC, OXA, VIM, IMP, NDM)	• Initiate contact precautions. • Consider infectious disease consult.

CTX-M indicates class A extended-spectrum beta-lactamases (Cefotaxime); IMP, imipenem-resistant metallo-beta-lactamase; KPC, *K. pneumoniae* carbapenemases; NDM, New Delhi metallo-β-lactamase; OXA, OXA-type beta-lactamases/class D beta-lactamases/oxacillinases; VIM, Verona integron-encoded metallo-beta-lactamase.

RESULTS

The patient demographic and laboratory data are summarized in *Table 2*. Overall, there was a slight predominance of women (61.2%) in the study cohort. The mean age of women was 56.6 ± 19.4 years, significantly lower ($P < 0.001$) than the mean age of the men (63.6 ± 15.9 years) at the time of the septic episode. This was unlikely to have any clinical significance. From the time of the blood collection, the Gram stain was reported within an average of 20.0 ± 10.4 hours and the BC-GN result was reported within 2.5 ± 1.3 hours of the Gram stain. The time between Gram stain and final identification and susceptibilities using conventional methods was 73.6 ± 40.0 hours.

The distribution of the GN bacterial targets across the three sites evaluated within the Baylor network is shown in *Table 3*. Across the three sites evaluated, *E. coli* was the predominant isolate (72.5%), 14.4% of which harbored extended spectrum beta-lactamases (ESBLs). This was followed by *Klebsiella* spp.,

Table 2. Demographic and laboratory parameters for result reporting (n = 899)

Parameter	Value	*P* value
Females: Males	550: 349	
Age (years), mean ± SD		
Overall	59.3 ± 18.5	
Male	63.6 ± 15.9	
Female	56.6 ± 19.4	<0.001
Time (hours), mean ± SD		
Between draw and Gram stain result	20.0 ± 10.4	
Between Gram stain and Gram-negative blood culture result	2.5 ± 1.3	
Between Gram stain and final report	73.6 ± 40.0	

Table 3. Distribution of Gram-negative organisms across three Baylor Scott & White Health hospitals

Targets	BUMC	BAS	IRV	Total
Escherichia coli	284	133	141	558
Klebsiella pneumoniae	94	31	26	151
Enterobacter spp.	37	12	4	53
Klebsiella oxytoca	8	2	4	14
Citrobacter spp.	4	5	0	9
ESBL producers				
E. coli (% ESBLs)	55 (19.4%)	14 (10.5%)	25 (17.7%)	94 (16.9%)
K. pneumoniae (% ESBLs)	16 (17.0%)	2 (6.5%)	0 (0%)	18 (11.9%)
K. oxytoca (% ESBLs)	1 (12.5%)	0 (0%)	0 (0%)	1 (7.1%)
Carbapenamase producers				
Enterobacter spp. (% carbapenamase producers)	1 (2.7%)	0 (0%)	0 (0%)	1 (1.9%)
Total	500	199	200	899

BAS indicates Baylor All Saints; BUMC, Baylor University Medical Center; ESBL, extended spectrum beta-lactamases; IRV, Baylor Irving.

which constituted 20.5% of the isolates, with 10.3% of the *Klebsiella* spp. harboring ESBLs.

The timeline of antibiotic adjustment in response to stewardship recommendations on the rapid BC-GN report is shown in *Figure 1*. Across all three sites combined, 29.1% (262/899) of patients were transitioned from empiric to targeted therapy and made the expected change to antibiotics in response to stewardship recommendations within 24 hours. In the subset where an intervention was made, the switch to appropriate targeted antibiotics was made at 12.2 ± 13.5 hours in response to BC-GN results, which was significantly earlier ($P < 0.001$) than when results by conventional methods became available (73.6 ± 40.0 hours).

After accounting for patients already on recommended targeted therapy, polymicrobial infections, and patients deceased or lost to follow-up, we found antibiotic stewardship opportunities in ~28% of GN infections. Further subanalysis demonstrated site-specific differences in the uptake of stewardship recommendations, whereby 32.4% of cases at Baylor University Medical Center, 50.5% at Baylor All Saints, and 15.0% at Baylor Irving demonstrated the expected change in antibiotics *(Table 4)*. We also noticed overuse of carbapenem/quinolone drug categories (only 9.6% of patients on carbapenem/quinolone were ESBL producers) at the Baylor Irving site.

DISCUSSION

Rapid identification of GN bacteremia and key susceptibility markers can lead to many benefits, such as earlier deescalation of empiric therapy and switch to appropriate targeted antimicrobials that can lead to better patient outcomes, decreased length of hospital stay, and decreased overall hospital costs (9–12). The Verigene BC-GN assay has two major advantages favoring its routine use: a random-access format with very limited hands-on time and the ability to rapidly provide clinically actionable therapeutic information to physicians.

Our study demonstrated that implementation of the BC-GN panel across a multisite facility led to earlier deescalation of empiric therapy and switch to appropriate targeted antibiotics in approximately 29% of the cases. Multiple patients were shown to be on targeted antibiotic therapy from initial dosing (i.e., before organism identification was available by Verigene BC-GN). The initial postulation was that the choice of antibiotics may be driven by order sets in the EHR, for which physicians may be directed to empiric therapy other than vancomycin and

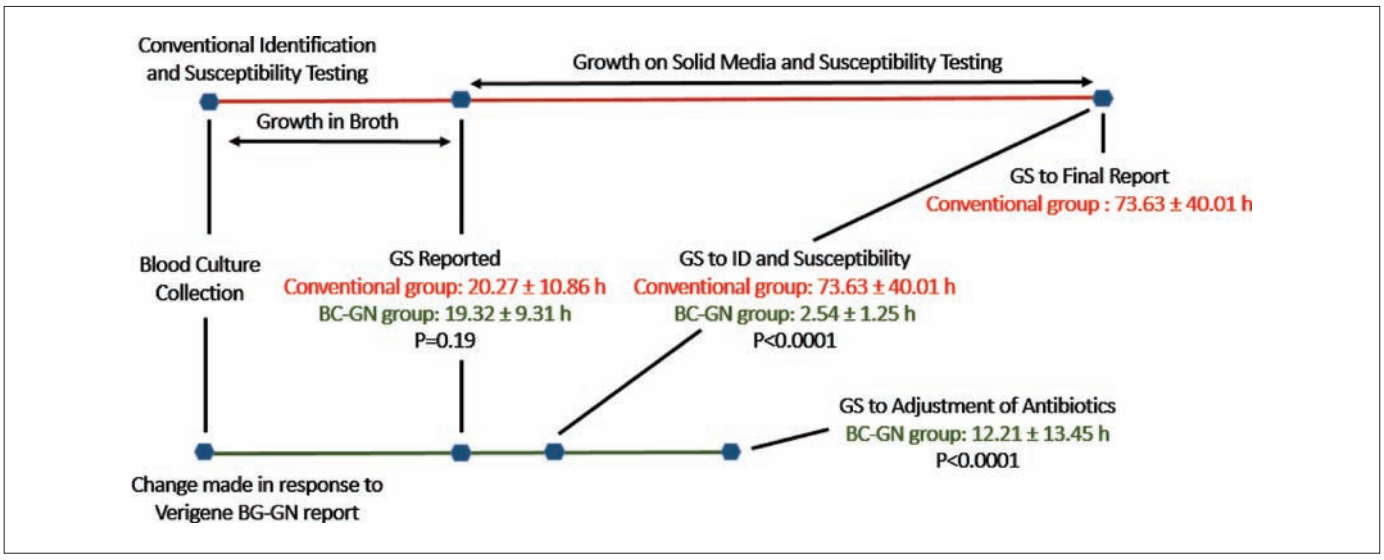

Figure 1. Overall timeline comparison between the following groups: response to final blood culture results by conventional identification and susceptibility methods as surrogate for adjustment of antibiotics in the conventional group vs. response to the preliminary identification and resistance marker reporting after BC-GN panel implementation. All times are listed as mean ± standard deviation in hours. ID indicates identification; GS, Gram stain; BC-GN, Gram-negative blood culture.

Table 4. Blood culture Gram-negative report utilization across three Baylor Scott & White Health hospitals

Parameter	Category	BUMC (n = 500)	BAS (n = 199)	IRV (n = 200)	Total (n = 899)
Expected change in antibiotics*		132 (26.4%)	100 (50.5%)	30 (15.0%)	262 (29.1%)
No change/change other than recommended		368 (73.6%)	99 (49.5%)	170 (85.0%)	637 (70.9)
Reasons for no change in GP coverage	Not on dedicated GP coverage	170 (34.0%)	26 (13.0%)	133 (66.5%)	329 (36.6%)
	Died/ED/discharged	35 (7.0%)	4 (2.0%)	0 (0.0%)	39 (4.3%)
	Polymicrobial cultures	31 (6.2%)	1 (0.5%)	2 (1.0%)	34 (3.8%)
	Continued empiric GP	132 (26.4%)	68 (34.0%)	35 (17.5%)	235 (26.1%)
Reasons for no change in GN coverage	On recommended antibiotics	53 (10.6%)	24 (12.0%)	82 (41.0%)	159 (17.7%)
	On other targeted antibiotics (carbapenem/quinolone)	55 (11.0%)	22 (11.0%)	73 (36.5%)	150 (16.7%)
	N (%) ESBLs	47/55 (85.5%)	16/22 (72.7%)	7/73 (9.6%)	70/150 (46.7%)
	Died/ED/discharged	35 (7.0%)	4 (2.0%)	0 (0.0%)	39 (4.3%)
	Polymicrobial cultures	31 (6.2%)	1 (0.5%)	2 (1.0%)	34 (3.8%)
	Continued empiric GN	194 (38.8%)	48 (24.0%)	13 (6.5%)	255 (28.4%)

BAS indicates Baylor All Saints; BUMC, Baylor University Medical Center; ED, emergency department; ESBL, extended spectrum beta-lactamases; GN, Gram-negative; GP, Gram-positive; IRV, Baylor Irving.

*Expected change was defined as deescalation of empiric therapy (vancomycin and piperacillin/tazobactam) for patients with *Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp., and *Escherichia coli* bacteremia to the appropriate targeted coverage per institutional guidelines within 24 hours in response to the stewardship recommendations on the Verigene report.

piperacillin/tazobactam, as it is not needed in all cases. However, further subset analysis by order sets demonstrated that there was no association between use of order sets to prescribe antibiotic therapy and changes in therapy in response to BC-GN result. There was also no association of patient location (i.e., within or outside of the intensive care unit) and response to the BC-GN results (data not shown).

We determined that there were site-specific differences in antibiotic stewardship practices. Of interest, we identified high empiric use of carbapenem/quinolone drug classes despite low identification of ESBL on the BC-GN result at the Baylor Irving site. Although carbapenems are active in this setting, these high-cost agents should be reserved for the additional coverage of drug-resistant organisms (13, 14). The outcome of this study will allow concentration of antimicrobial stewardship efforts at this site. Confidence in the rapid results on non-ESBL producers on the BC-GN panel combined with education should minimize the use of carbapenem/quinolone drug categories when not indicated. Further opportunities for discontinuation of empiric coverage and earlier switch to targeted therapy were identified for approximately one-fourth of the cases.

Our study is comparable to previously published outcome studies on BC-GN rapid testing. Hill et al (10) evaluated the performance of the Verigene BC-GN assay and potential impact of rapid antibiotic interventions in 54 patients. BC-GN identified the organism approximately 24 hours faster than conventional methods. Upon retrospective evaluation of medical records by the stewardship team, it was concluded that antibiotic management could have been modified for 31.8% of patients an average of 33 hours sooner. Walker et al (12) did a retrospective review of GN bacteremia cases before (n = 98) and after (n = 97) Verigene BC-GN implementation and demonstrated that rapid implementation of effective therapy was statistically significant for postintervention cases of ESBL-producing organisms ($P = 0.049$) but not overall ($P = 0.12$).

The study was limited, as it did not evaluate the economic savings to the hospital in terms of antibiotic usage, length of hospitalization, and mortality. Another limitation is that underlying diagnosis and associated complications were not evaluated. Larger prospective studies are warranted to support the findings of our study and to address other important aspects influencing the routine use of this assay.

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