Validation of an Antimicrobial Stewardship-Driven Verigene Blood-Culture Gram-Negative Treatment Algorithm to Improve Appropriateness of Antibiotics

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Abstract

Rapid diagnostic testing (RDT) allows for early adjustment of antibiotic therapy. This study examined the potential impact of a stewardship-driven antibiotic treatment algorithm, incorporating RDT into the management of Gram-negative bacteremia. The proposed algorithm would have resulted in 88.4% of cases receiving appropriate antibiotic therapy versus 78.1% by standard of care (P = .014).

Keywords: diagnostic stewardship; multiplex PCR; rapid diagnostic.

Gram-negative bacteremia (GNB) is associated with significant morbidity and mortality [1]. Timely, appropriate antibiotic therapy is paramount to improving clinical outcomes in GNB [2, 3]. The Verigene Blood-Culture Gram-Negative (BC-GN) is a rapid diagnostic test (RDT) that identifies 8 target GN organisms (Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Pseudomonas aeruginosa, Acinetobacter spp, Citrobacter spp, Enterobacter spp, Proteus spp) and 6 resistance determinants (CTX-M, IMP, KPC, NDM, OXA, and VIM) within 2.5 hours of Gram-stain [4]. The Verigene BC-GN has a reported sensitivity and specificity for GN organism identification of 97.1% (95% confidence interval [CI], 90.7%–98.4%) and 99.5% (95% CI, 98.8%–99.8%), respectively [5].

Unlike the Verigene BC Gram-Positive, there is sparse literature to help guide clinicians on how to optimally incorporate the Verigene BC-GN into clinical practice and support antimicrobial stewardship (AMS) initiatives [6–8]. In a recent study, Rivard et al [6] reported significant reductions in time to effective antibiotic therapy and length of stay, but not inpatient mortality, with a Verigene BC-GN treatment algorithm and active AMS intervention at a large multicenter health system. This current study sought to validate a proposed treatment algorithm developed for use with Verigene BC-GN results in a retrospective cohort of patients with GNB.

METHODS

This was a retrospective, single-center, observational study of adult patients (≥18 years) with GNB at our 800-bed academic tertiary care hospital from September 2015 to May 2016. This research involved medical chart review of human participants and was completed in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration.

Treatment Algorithm Development

An AMS-driven treatment algorithm for GNB in adults was developed based on institution-specific antibiogram data combined with evidence-based practice for management of drug-resistant GN organisms (Supplement 1) [9–11]. Cutoff values of 88% susceptible or higher were used to determine acceptable antibiotic recommendations for each target GN organism if a resistance mechanism was not identified by Verigene BC-GN. This cutoff was established based on reported susceptibility of P aeruginosa to piperacillin-tazobactam, our institutional workhorse antipseudomonal antibiotic agent. Among patients with solid organ transplant or admitted to an intensive care unit with E coli or Klebsiella spp, our antibiogram data showed consistently higher rates (>15%) of third-generation cephalosporin resistance. Given the possibility of such resistance being mediated by non-CTX-M β-lactamases not detected by Verigene BC-GN, use of meropenem (until susceptibility results) was recommended due to the potential risk associated with inappropriate antibiotic de-escalation in these patient populations. A disclaimer was added to the algorithm that recommendations should not supersede clinical judgment based on patient-specific risk factors and history.

Validation of Treatment Algorithm

Routine clinical reporting of Verigene BC-GN began in September 2015. Patients were included for analysis if at least 1 blood culture was positive for a GN organism as identified by the University of Maryland Medical Center (UMMC) Clinical Microbiology Laboratory; patients were only included once during the study period. Patients’ clinical characteristics, comorbidities, and antibiotics administered as part of standard care were collected through electronic medical chart review.
Standard care GN antibiotic therapy was defined as receipt of an antibiotic agent with GN activity within 12 hours of Verigene BC-GN reporting and before susceptibility reporting.

Before assessment of antibiotic therapy by standard care versus algorithm recommendations, 2 investigators (K.C.C. and E.L.H.), both AMS pharmacists, met to define appropriateness. Appropriateness of antibiotic therapy was first determined by assessment of in vitro susceptibility testing following the Clinical and Laboratory Standards Institute guidelines wherein therapy would be inappropriate if the organism was determined to be resistant or intermediate to the antibiotic agent. In addition, appropriate antibiotics were those that were not overly broad in spectrum (ie, meropenem for pan-susceptible *E coli*) or did not account for the potential of inducible resistance (ie, AmpC induction *Enterobacter* or *Citrobacter* spp). Assessment of allergy history or past history of antibiotic-resistant isolates was not considered for this assessment. Appropriateness of antibiotics received per standard care was compared with theoretical receipt of antibiotics guided by the UMMC AMS treatment algorithm. K.C.C. and E.L.H. independently evaluated appropriateness of both standard care and algorithm antimicrobial recommendations.

Overall interrater agreement on appropriateness of standard care versus algorithm-recommended antibiotics was assessed using Cohen’s kappa statistic. Comparisons and associations between inappropriate antibiotic recommendations and patient characteristics were completed using χ² or Fisher’s exact test. All statistical analyses were completed using SPSS Statistics (Version 24.0; IBM Corp., Armonk, NY).

### RESULTS

During the study period, 256 cases of GNB were screened and a total of 188 patients with GNB were included in the final analysis; 144 (76.5%) were positive for Verigene BC-GN target organisms. The most common reasons for study exclusion were age <18 years and lack of availability of data (pre-electronic medical record). The mean age of patients with GNB was 54.5 years (standard deviation, 15.5 years), the most common source of GNB was genitourinary, and *E coli* was the most common Verigene BC-GN target organism identified (Table 1). Overall, in vitro susceptibility was higher with algorithm-recommended antibiotics compared with standard care (92.1% versus 77.8%) for those isolates that could be assessed.

| Source of GNB | Central line | Endocarditis | Gastrointestinal/intra-abdominal | Genitourinary | Skin and soft tissue | Respiratory | Unclear | Polymicrobial bloodstream infection (any) | Polymicrobial GNB | Verigene Organism Identification | Acinetobacter spp | Proteus spp | Pseudomonas aeruginosa | Klebsiella pneumoniae | Klebsiella oxytoca | Escherichia coli | Enterobacter spp | Citrobacter spp | Nontarget | Verigene Resistance Determinant | OXA | CTX-M | KPC |
|---------------|--------------|--------------|---------------------------------|---------------|---------------------|-------------|---------|--------------------------------------|-----------------|-------------------------------|----------------|-------------|------------------------|------------------|-----------------|----------------|-----------------|----------------|----------|------------------------|-----|-------|------|
| n             | 21 (11.2)    | 4 (2.1)      | 33 (17.6)                       | 55 (29.3)     | 14 (7.5)            | 21 (11.2)   | 30 (16.0) | 24 (12.8)                           | 8 (4.3)         | 10 (5.3)                        | 7 (3.7)        | 21 (11.2)  | 26 (13.8)                  | 3 (1.6)          | 56 (29.9)        | 18 (9.6)      | 2 (1.1)         | 45 (23.9) | 8 (4.3) | 4 (2.1) |

Table 1. Patient Clinical Characteristics

| Age (Years) | 54.5 (±15.5) |
|-------------|--------------|
| Male        | 116 (62.2)   |
| ICU at time of GNB | 65 (45.1) |
| Infectious disease consult | 157 (85.8) |
| Past Medical History |              |
| Hemodialysis | 11 (5.9)   |
| Diabetes mellitus | 66 (35.1) |
| Any renal disease | 38 (14.9) |
| Resistant GNB organism |              |

Abbreviations: BC-GN, blood-culture Gram-negative; GNB, Gram-negative bacteremia; ICU, intensive care unit; KPC, Klebsiella pneumoniae carbapenemase; SD, standard deviation.

*Continuous data presented as mean (SD). Categorical data presented as n (%).

### CONCLUSIONS

This study demonstrated the ability to derive a treatment algorithm using institution-specific antibiogram data, evidence-based medicine, and Verigene BC-GN results, with the potential to increase the proportion of patients receiving timely appropriate antimicrobial therapy compared with standard care. Rivard et al [6] have demonstrated potential benefits of a treatment algorithm incorporating Verigene BC-GN, including decreased time to effective and appropriate therapy in addition to decreased hospital length of stay. In addition, our group, in collaboration with researchers at the Detroit Medical Center,
recently published a blueprint for AMS to develop Verigene BC-GN organism and resistance determinant-specific antibiograms based on institutionally derived and validated data [12]. Together, these publications help to reinforce the potential benefits of actively incorporating RDTs in to routine AMS practices.

Our findings are also consistent with studies showing the incremental value of AMS interventions in conjunction with RDTs. Timbrook et al [1], in their 2017 meta-analysis, demonstrated decreased mortality only in the subgroup of studies where AMS was actively involved (odds ratio [OR] = 0.64 [95% CI, 0.51–0.79] versus OR = 0.72 [95% CI, 0.46–1.22] without AMS intervention). As mentioned, Rivard et al [6] demonstrated that improved time to effective therapy among patients with GNB not receiving appropriate empiric therapy significantly decreased (median decrease from 24.5 to 8.8 hours from Gram-stain). In addition, in a randomized trial, Banerjee et al[13] reported decreased use of broad-spectrum antibiotics and significantly decreased time to appropriate de-escalation of antibiotics (21 hours with RDT + AMS versus 34 hours with control versus 38 hours RDT, P < .001).

An important consideration to the current study is that 100% algorithm adherence does have the potential for unnecessary escalation or inappropriate de-escalation of antibiotics. Being retrospective in nature, a limitation of the current analysis is that we are assuming changes in antibiotic therapy and not taking into account the full clinical picture for each patient (ie, source of infection, previous isolation of resistant GN organisms). Our institution decided to first validate an algorithm through theoretical receipt of recommended antibiotic agents as opposed to first implementing an algorithm and assessing outcomes secondary to the limited data on the use of Verigene BC-GN at the time of implementation. This is especially true with respect to de-escalation of antibiotic therapy. For instance, recommendations to de-escalate to ceftriaxone in *E coli* or *Klebsiella* spp that are CTX-M negative should be based on known institutional rates of CTM-X (ie, versus TEM or SHV). Future studies exploring the role of RDTs in the management of GNB, optimal decision-making strategies, and their potential clinical impact will become increasingly relevant in an era of increased cost-consciousness and growing antimicrobial resistance, with emphasis on both timely antibiotic therapy and AMS.

## 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.

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