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Evaluating the impact of Verigene® organism identification on antimicrobial stewardship recommendations

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Evaluating the Impact of Verigene® Organism Identification on Antimicrobial Stewardship Recommendations

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Evaluating the Impact of Verigene® Organism Identification on Antimicrobial Stewardship Recommendations

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Abstract

Introduction: Verigene® is one of many commercially available rapid diagnostic tests (RDT) for organism identification in blood culture. Community Health Network (CHNw) utilizes this system to identify blood cultures and guide antimicrobial therapy. As antibiotic resistance becomes more and more prevalent, limiting exposure to broad-spectrum antibiotic therapy is of paramount importance. RDT provides more timely information to providers, which if utilized appropriately, can result in the patient receiving appropriate antibiotic therapy in a shorter time and further limits unnecessary antibiotic exposure. CHNw evaluated the use of Verigene® beginning in 2017 which led to the initiation of provider and pharmacist education of proper Verigene® utilization.

Objectives: The primary objective of Aim 1 was to determine the accuracy of the Verigene® test by comparing its results to the identified organism's phenotypic susceptibility pattern. The primary objective of Aim 2 was to re-evaluate the use of Verigene® within CHNw. Secondary objectives were to compare all cause hospital mortality, 30-day readmission, hospital length of stay (LOS), and duration of inpatient antibiotics. The primary objective of Aim 3 was to compare Verigene® utilization across CHNw sites and to evaluate the impact of provider and pharmacist education compared to pharmacist education alone.

Methods: In this three-part, retrospective chart review, demographic and clinical information was collected from the electronic health record. Aim 1 data included clinical information such as Verigene® organism, Verigene® resistance genes, phenotypic organism and susceptibility data for target antimicrobials. Aim 2 and 3 data included demographic and clinical information such as antibiotic therapy, time of de-escalation, duration of inpatient antibiotics, and positive culture data. Patients 18-89 years of age with a positive, monomicrobic blood culture from July 1, 2015 to December 31, 2018 were included for Aim 1 and those with a positive blood culture for *Escherichia coli* from July 1, 2018 to December 31, 2018 were included for Aims 2 and 3.

Results: Aim 1 analyzed 2,052 isolates: 637 *Staphylococcus aureus*, 22 *Enterococcus* spp., 739 *Escherichia coli*, and 654 *Klebsiella pneumoniae*. Ceftriaxone resistance was present in 101 (13.7%) of *E. coli* and *K. pneumoniae* (excluding KPC genes) isolates and 81 (80.2%) of these were identified with the CTX-M resistance marker by Verigene®. Meropenem resistance was present in 8 (1.2%) of *K. pneumoniae* isolates and 3 (37.5%) of those were identified with KPC. Oxacillin resistance was present in 255 (40.0%) of *S. aureus* isolates and 254 (99.6%) of those were identified with MecA. Vancomycin resistance was present in 22 (100%) of *Enterococcus* spp. isolates and all were identified with VanA or VanB. Aim 2 showed Verigene® was utilized to de-escalate antimicrobials prior to phenotypic susceptibilities in 29 of 85 patients (34.1%). There was no statistically significant difference in all-cause mortality between the Verigene® utilized group and Verigene® not utilized group (5/29 (17.2%) vs. 7/56 (12.5%), p = 0.533). The mean duration of inpatient antibiotics did not vary significantly between groups (5.69 days SD ±2.055 in Verigene® utilized group vs. 6.25 days ±2.881 in Verigene® not utilized, p=0.305). Aim 3 results pending.

Discussion: The results of this study show that providers should have increased confidence in the utilization and accuracy of Verigene®; however, in the case of *E. coli* bacteremia, Verigene® is still not being utilized to de-escalate therapy despite educational efforts. More robust education or additional methods/resources are needed to improve the utility of Verigene® within CHNw.

Introduction

Verigene® is one of many commercially available rapid diagnostic tests (RDT) for organism identification in blood culture. Verigene® tests utilize NanoGrid technology to detect DNA or RNA targets using nucleic acid extraction and PCR amplification. The nucleic acids are automatically transferred to a Verigene® test cartridge for primary and secondary hybridization where oligonucleotides are captured on a microarray and amplified for automated qualitative analysis.[1] The Verigene® blood culture gram-positive (BC-GP) assay can identify unique *Staphylococcus, Streptococcus, Enterococcus*, and *Listeria* species including the resistance markers MecA (denotes methicillin-resistant *S. aureus* (MRSA)), and VanA and VanB (denotes vancomycin resistance in *Enterococci)*. The Verigene® blood culture gram-negative (BC-GN) assay can identify *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Pseudomonas aeruginosa, Acinetobacter* species, *Proteus* species, *Citrobacter* species and *Enterobacter* species including the resistance markers for *Klebsiella* producing carbapenemase (KPC), New Delhi metallo-beta-lactamase (NDM), Cefotaxime hydrolyzing enzyme (CTX-M), Verona integrin-encoded metallo-beta-lactamase (VIM), Imipenem hydrolyzing enzyme (IMP) and Oxacillin hydrolyzing enzymes (OXA) genes. These genes target commonly encountered and/or clinically challenging beta-lactamases that can readily hydrolyze a wide variety of beta-lactam antibiotics, including carbapenems, piperacillin-tazobactam, and cefepime, respectively.[2, 3]

Laboratory testing using traditional methods such as Gram staining and culture-based techniques require 24-72 hours for results to return before optimal antimicrobial therapy can be determined. Verigene® is an RDT that identifies the genus, species, and select beta-lactamase resistance determinants for select pathogens within 2-3 hours.[2, 4] This RDT allows providers and antimicrobial stewardship teams to make timely decisions to optimize antibiotic therapy and potentially improve patient outcomes.[5] If interpreted correctly and used promptly, implementation of RDTs have demonstrated the ability to decrease: time to effective therapy, cost, length of stay, and mortality.[6]

Antimicrobial resistance is a global issue that is threatening our ability to adequately treat common infectious diseases. Resistance occurs when microorganisms adapt and develop resistance mechanisms in the presence of antimicrobial drugs. As antibiotic resistance becomes more and more prevalent, limiting exposure to broad-spectrum antibiotic therapy is of paramount importance. Rapid diagnostic tests provide more timely information to providers, which if utilized appropriately, can result in the patient receiving appropriate antibiotic therapy in a shorter time and further limits unnecessary antibiotic exposure.[6, 7] The incidence of multidrug-resistant (MDR) organisms causing bloodstream infections is increasing.[8] A recent review cited that RDT in combination with antimicrobial stewardship intervention can produce positive outcomes in regards to patient care, overall health care costs, and antimicrobial stewardship.[6]

Community Health Network (CHNw) utilizes Verigene® to identify blood cultures and guide antimicrobial therapy. Verigene® testing is automatically performed on the first monomicrobial, aerobic blood culture of a particular patient within CHNw. CHNw evaluated the use of Verigene® in 2017-2018. In this previous evaluation, it was found that 71% of Verigene® use was appropriate. It was further discovered that an infectious disease consult improved the use of Verigene® while a blood culture with a gram-negative organism limited its use. This information led CHNw to embark upon a multi-faceted initiative to further improve the use of Verigene® as well as reduce the use of anti-pseudomonal beta-lactams across CHNw.

Methods

This was a three-part, retrospective chart review to determine the microbiological accuracy of Verigene® within CHNw and evaluate the use of Verigene® organism identification regarding antimicrobial de-escalation of *Escherichia coli* bacteremia. This data was then used to compare utilization across CHNw sites based on those who received provider and pharmacist education versus pharmacist education alone. CHNw consists of 5 primary hospitals (Community Hospital: East (CHE), North (CHN), South (CHS), Heart and Vascular (CHVH), and Howard

Regional (CHRH) in the greater Indianapolis, IN area. Each of the 5 hospitals is its own distinct entity, with a diverse patient population.

The study population consisted of patients from CHE, CHN, CHS, CHVH and CHRH. CHRH was not included in Aim 3 due to inability to control the type and level of provider education provided at this site. A patient list was generated from a third-party decision support program (Vigilanz®) that included patients with both a positive Verigene® result as well as phenotypic susceptibilities. The list was limited to only the organisms of interest as defined by the inclusion criteria for each aim. Exclusion criteria for all 3 aims were patients with polymicrobial bacteremia or on antimicrobials with known culture and susceptibilities at the time of admission, hospice or palliative care patients, patients <18 years or >89 years old, pregnant, incarcerated, and behavioral care patients.

Aim 1

The initial aim of this study was to determine the accuracy of the Verigene® test by comparing its results to the identified organism's phenotypic susceptibility pattern and determining the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Verigene® organism identification and presence/absence of resistance genes detected by Verigene® for antimicrobial susceptibility compared to target antimicrobials.

This aim was a retrospective chart review evaluating patients with positive blood cultures for *Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, and *Klebsiella pneumoniae* from July 1, 2015 to December 31, 2018. Data collection consisted of the Verigene® organisms and any resistance targets detected and the phenotypic susceptibility results for this organism. Regarding *Staphylococcus aureus*, we compared the presence/absence of the MecA gene and the phenotypic susceptibility to oxacillin. In *Enterococcus* spp, we compared the presence/absence of the VanA or VanB gene and the phenotypic susceptibility to vancomycin. In reference to *Escherichia coli* and *Klebsiella pneumoniae,* we compared the presence/absence of CTX-M and

KPC and the phenotypic susceptibility to ceftriaxone and meropenem and/or ertapenem, respectively.

Inclusion criteria: Patients 18-89 years of age who had positive, monomicrobic blood cultures between July 1, 2015-December 31, 2018. Only the first blood culture per patient per visit was included. The blood culture had to contain both a Verigene® result and phenotypic antimicrobial susceptibilities. Only cultures with the following target organisms were included: *Staphylococcus aureus, Enterococcus* spp., *Escherichia coli*, and *Klebsiella pneumoniae*.

Aim 2

The second aim of this project was to re-evaluate the utilization of Verigene® results in regard to antimicrobial de-escalation of *Escherichia coli* bacteremia within CHNw. Secondary objectives were to compare all cause hospital mortality, 30-day readmission, hospital length of stay (LOS), and duration of inpatient antibiotics.

This was a retrospective comparative chart review evaluating Verigene® use within CHNw. Data for this aim was collected through EPIC, the electronic medical record utilized in CHNw. Demographics, comorbidities, Charlson comorbidity index, antimicrobial allergies, antimicrobial ordering provider service, presence of an infectious disease consult, Verigene® identification results, phenotypic susceptibilities, time of de-escalation, 30-day infection related readmission, and all-cause mortality during hospitalization were collected. Categories of de-escalation were defined as either Verigene® utilized (de-escalation of antimicrobial therapy prior to susceptibilities) or Verigene® not utilized (de-escalation of antimicrobial therapy after susceptibilities resulted).

Inclusion criteria: Patients 18-89 years of age who were admitted to any CHNw site with a positive, monomicrobic blood culture for *Escherichia coli* and initiated on antibiotic therapy between July 1, 2018-December 31, 2018.

Aim 3

The final aim was a retrospective comparative chart review using data from the post-education cohort included in Aim 2 compared to previous data to determine if the education initiative improved the use of Verigene®. Educational efforts on Verigene® and its interpretation were provided to key prescribers at CHE, CHN and CHVH, as well as clinical pharmacists at these sites. Educational efforts at CHS only consisted of pharmacists due to inability to get provider education scheduled. We compared Verigene® use at CHE, CHN, and CHVH with CHS. Thus, this aim also evaluated the impact of provider and pharmacist education compared to pharmacist education alone.

Inclusion criteria: Patients 18-89 years of age who were admitted to any CHNw site with a positive, monomicrobic blood culture for *Escherichia coli* and initiated on antibiotic therapy between July 1, 2018-December 31, 2018.

Statistical Analysis

Descriptive statistics were utilized for baseline characteristics and the primary and secondary outcomes in the post education group. Statistical analyses between pre- and post-educational groups were compared using the Pearson chi-square test or the Fisher exact test for dichotomous variables and a student's t-test for continuous variables. A P value of 0.05 was considered statistically significant. All study data were collected and managed using Excel. Statistical analysis was completed using Statistical Package for the Social Sciences software, version 23.0 (IBM Corp., Armonk, NY).

Results

Aim 1

Positive monomicrobic blood cultures for *Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, and *Klebsiella pneumoniae* were obtained from 2,052 positive blood cultures. Of the 2,052 isolates, 637 (31.0%) were analyzed for the target antimicrobial, oxacillin, 22 (1.1%) for vancomycin, 739 (36.0%) for ceftriaxone, and 654 (31.9%) for meropenem. Resistance

determinants were seen in 386 (18.8%) isolates consisting of 101 CTX-M, 8 KPC, 255 MecA, and 22 VanA or VanB. Table 1 describes the rates of resistance to target antimicrobials, frequency of Verigene® identification of resistance markers, sensitivity, specificity, PPV, and NPV. Ceftriaxone resistance was present in 101 (13.7%) of *E. coli* and *K. pneumoniae* isolates, excluding those with KPC genes, and 81 (80.2%) of these were identified with the CTX-M resistance marker by Verigene®; therefore, the NPV was 97.0%. Denoting that 97% of *E. coli* isolates were susceptible to ceftriaxone in the absence of the CTX-M gene by Verigene®. Meropenem resistance was present in 8 (1.2%) of gram-negative isolates and 3 (37.5%) of those were identified with the KPC resistance marker by Verigene®; therefore, the NPV was 99.2%. Ertapenem results were inconsistent; therefore, only meropenem susceptibility was used for KPC markers. Oxacillin resistance was present in 255 (40.0%) of *S. aureus* isolates and 254 (99.6%) of those were identified with the MecA resistance marker by Verigene®; therefore, the NPV was 99.7%. Vancomycin resistance was present in 22 (100%) of *Enterococcus* spp. isolates and all were identified with the VanA or VanB resistance markers by Verigene®. The NPV was unable to be calculated because all resistance markers were identified correctly.

Table 1: Verigene® Results by Target Drug

Target Drug	N	Resistance Marker	N (%) Resistant	N Identified by Verigene	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ceftriaxone	739	CTX-M	101 (13.7)	81	80.2	99.8	98.8	97.0
Meropenem	654	KPC	8 (1.2)	3	37.5	100	100	99.2
Oxacillin	637	MecA	255 (40.0)	254	99.6	100	100	99.7
Vancomycin	22	VanA/VanB	22 (100)	22	100	N/A	100	N/A

NPV = negative predictive value; PPV = positive predictive value

Aim 2

From July 1, 2018 to December 31, 2018, 88 patients were admitted to CHNw with a positive, monomicrobic blood culture for *Escherichia coli* and initiated on antibiotic therapy. Three patients were excluded from analysis due to hospice care. Of the remaining 85 patients, 57 (67.1%) were female and 28 (32.9%) were male. Verigene® was utilized to de-escalate antimicrobials appropriately (prior to phenotypic susceptibilities) in 29 of 85 patients (34.1%)

with *Escherichia coli* bacteremia. There was no statistically significant difference in all-cause mortality between the Verigene® utilized group and Verigene® not utilized group (5 of 29 (17.2%) vs. 7 of 56 (12.5%), p = 0.533). The difference between readmission within 30 days for an infectious disease related cause was not statistically significant (Table 2). Additionally, the mean duration of inpatient antibiotics and length of stay (LOS) did not vary significantly between groups (Table 2). The duration of antibiotics was measured in days of therapy. If patients received more than one antibiotic, each day of therapy of each drug was counted separately and added to the total; therefore, mean duration of antibiotics accounts for more days than LOS.

Table 2: Mean Duration of Antibiotics, Length of Stay, and 30-Day Readmission

Secondary Objective	Verigene® Utilized		Verigene® Not Utilized		p value
	mean (days)	SD	mean (days)	SD	
Duration of Inpatient Antibiotics	5.69	± 2.055	6.25	± 2.881	0.305
LOS	4.97	± 2.179	3.933	± 3.933	0.290
30-Day Readmission	2 patients	7.1%	3 patients	5.4%	1.000

SD = Standard Deviation

Aim 3

Results pending.

Discussion

For all target antibiotics except meropenem, susceptibility was largely predicted by the presence/absence of the resistance determinants identified by Verigene®. In the case of meropenem, the sensitivity of KPC gene alone was not high enough to predict resistance. This suggests that meropenem resistance was mediated by another mechanism(s). It is well known that meropenem resistance can occur with a combination of an altered target site mutation and an efflux pump, without the presence of a beta-lactamase enzyme.[9] Although there was a small sample of *Enterococcus* spp. isolates, it is encouraging that Verigene® was able to identify the resistance marker in all 22 samples. In the case of MecA and CTX resistance, the probability of resistance was 40% and 13.7% respectively; however, the NPV values were 99.7% and 97%. This should give providers the reassurance that only up to 3% of isolates will be resistant if the

test is negative. By assessing the accuracy of Verigene® within CHNw, providers may have an increased confidence in the utilization of this test which could help limit the use of broad-spectrum antimicrobials. To further optimize therapy and improve providers' comfort with Verigene® utilization, an antibiogram can be developed to display percentages of antimicrobial susceptibility of target organisms to key antimicrobial agents based on the presence or absence of resistance markers. Limitations of this analysis include small sample size of certain isolates and lack of generalizability based on one institution. This information should be analyzed frequently as mechanisms of resistance can change over time in any given geographic location. This study is comparable to published studies analyzing the performance of Verigene®. Bork et al[10] evaluated 137 isolates of varying gram-negative organisms, including *K. pneumoniae* (n = 36) and *E. coli* (n = 35). Of the resistant organisms, Verigene® detected 1 of 3 CTX-M genes for *E. coli* and 4 of 5 CTX-M genes for *K. pneumoniae*. Pogue et al[5] analyzed 1,046 gram-negative blood cultures at two institutions, including 489 *E. coli* isolates and 197 *K. pneumoniae* isolates. Regarding CTX-M and KPC resistance genes of these two organisms, NPV ranged from 93 to 100%.

Upon reviewing the utilization of Verigene®, a majority (65.9%) of patients' antimicrobials were not de-escalated until phenotypic susceptibilities resulted. Additionally, an infectious disease consult did not significantly improve the use of Verigene®, which differed from our pre-educational cohort. While the results of this cohort were not directly compared to historical data of the pre-educational cohort at the time of this writing, the initial educational effort did not seem to improve the utility of the Verigene® test. The lack of significant differences in Verigene® use seen in Aim 2 of this study, which was also reported in the pre-educational cohort, suggests that these educational efforts were not effective or did not reach enough providers to improve uptake of these results; therefore, more robust education or additional methods/resources are needed to improve the utility of Verigene® within these hospitals. Aim 3 analysis is pending; however, it may provide insight as to whether provider

education made any difference in Verigene® use in the current cohort and whether education is a reliable method for implementing change at these hospital sites.

Conclusion

As rapid diagnostic testing becomes more widely used within health institutions, it is important that future studies continue to analyze the accuracy and clinical utility of testing results. This study helps to highlight the utility of Verigene® within CHNw. Based on these results, providers at CHNw should feel comfortable de-escalating antimicrobial therapy when Verigene® does not detect any resistance markers. As the use of Verigene® continues to grow, additional organisms can be analyzed to establish further credibility.

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