
Clinical Outcomes with Implementation of Accelerate Pheno™ Blood Culture Detection System for Gram-Negative Bacteremia

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Abstract: Delayed treatment in bacteremia increases patient morbidity and healthcare costs. Accelerate Pheno™ Blood Culture Detection System (AXDX) is a novel diagnostic technology for the rapid detection of gram-negative bacteremia. Studies have shown accurate and faster time to speciation and sensitivity (TTSS) by AXDX compared to conventional modality. However, however, our study further examined the direct impact of AXDX on clinical outcomes and cost. Our retrospective study consisted of 178 patients at least 18 years old admitted to our academic medical institution with gram-negative bacteremia. The pre-AXDX group had 91 patients admitted in 2019 while the post-AXDX group had 87 patients admitted in 2021. Demographics, microbes, TTSS, time to de-escalation of therapy (TTDeT), length of stay (LOS), readmissions, and *Clostridioides difficile* infection (CDI) rates were recorded and differences between the cohorts were statistically analyzed. The pre-AXDX group had 51.32% females, mean age of 60.28 years, mean Charlson Co-morbidity Index (CCMI) of 2.23, mean LOS of 21.19 days, and mean Pitt-Bacteremia Score (PBS) of 2.35. The post-AXDX group had 51.92% females, mean age of 63.66 years, mean CCMI of 2.99, median LOS of 15.02 days, and mean PBS of 2.71. Both groups' top two sources of bacteremia were urinary and gastrointestinal and the two most common microbes were *Escherichia coli* and *Klebsiella pneumoniae*. Pre-AXDX's mean TTSS was 70.95 hours and 62.92 hours for post-AXDX. Pre-AXDX's mean TTDeT was 73.90 hours and 43.85 hours for post-AXDX. The pre-AXDX cohort had 7.12% increase in related readmissions, 5.45% more CDI, and 0.26% increase in inpatient mortality. In addition to faster TTSS with AXDX as seen with previous studies, our study shows clinical advantages with AXDX use. While both groups were comparable in bacteremia sources and microbes. The post-AXDX group had higher CCMI and PBS scores, indicating they were more ill. Despite this, the pre-AXDX group had longer TTDeT by 30.05 hours, longer mean LOS by 6.17 days, 5.45% more CDI, 7.12% more readmissions, and 0.26% more mortality rates. The pre-AXDX group also reported adverse reactions to antibiotics while the post-AXDX had none. Our data shows AXDX use improves clinical outcomes with fewer adverse effects, mortality, and CDI

rates and decreases cost with shorter LOS and lower readmission rates.

Keywords: Gram-Negative Bacteremia, Rapid Diagnostic Technology, Outcomes, Costs

1. Introduction

Sepsis continues to be a major healthcare burden. It remains the most common diagnosis for hospital admissions leading to healthcare costs as high as \$23.7 billion [33-35]. Mortality from sepsis contributes to 30% to 50% of hospital deaths [15, 21, 22]. Sepsis secondary to gram-negative bloodstream infections (GN-BSI) was shown to be a contributing cause of death. Additionally, patients with GN-BSI have a significantly lower five-year survival rate [36]. Initiating early and appropriate antimicrobial therapy is the mainstay management for decreasing morbidity and mortality in patients with sepsis [12, 20]. Delayed appropriate therapy is associated with 70% longer stays, 65% more expensive hospital costs, and 20% higher risk for mortality [5]. There are innovative rapid diagnostic technologies for microbial identification and antimicrobial sensitivities to improve outcomes [16, 26]. The Accelerate Pheno™ Blood Culture Detection System (AXDX) is one of the newer rapid diagnostic technologies available. Based on Accelerate Diagnostics, AXDX utilizes fluorescence in-situ hybridization for microbial detection, identification, and quantification with the average time for antibiotic susceptibility time (AST) being approximately 7 hours and the identification time being 2 hours [1]. Since its FDA clearance in February 2017 and subsequent approval in September 2020, there have been many studies evaluating the performance of AXDX relative to conventional laboratory techniques. Most of these studies confirm that this new technology provides microbial identification and antibiotic sensitivity much quicker while maintaining accuracy compared to conventional laboratory techniques [2, 4, 6-9, 14, 23, 29-31]. Some studies predicted the potential changes to timing for appropriate and definitive antimicrobial therapies and the likely impacts on patient clinical outcomes. Our study is unique in that we examine the direct impact of AXDX on clinical outcomes and cost.

2. Materials and Methods

2.1. Study Design and Participants

This study included non-pregnant participants over the age of 18 years old who were admitted in 2019 and 2021 with gram-negative bacteremia to an academic tertiary hospital. The participants were grouped into a pre-AXDX implementation cohort, which comprised patients admitted in 2019. West Virginia University Microbiology Laboratory implemented AXDX in January 2021 and the post-AXDX implementation cohort consisted of patients admitted in 2021. Two hundred participants were initially identified by the clinical microbiology laboratory at Ruby Memorial

Hospital in Morgantown, West Virginia. There were 22 patients excluded due to polymicrobial organism growth in blood cultures, or less than 24 hours length of stay (LOS) due to in-hospitalization mortality or transfer to another facility. After exclusion, 91 patients were in the pre-AXDX cohort and 87 patients were in the post-AXDX cohort. Demographics, microbes, TTSS, time to de-escalation of therapy (TTDeT), length of stay (LOS), and readmissions and *Clostridioides difficile* infection (CDI) rates were recorded.

2.2. Microbiological Data Collection

Our clinical microbiology laboratory is a College of American Pathologists accredited facility that offers a comprehensive testing menu and serves as the primary infectious diseases diagnostic reference lab for all hospital laboratories within the West Virginia University Medicine health system (WVUMed).

Orders for adult blood cultures for all WVUMed patients automatically prompt the collection of two culture sets from two separate venipuncture sites, each of which contains one aerobic and one anaerobic bottle (FA Plus and FN Plus, BioMeriueX, Durham, NC). All bottles are obtained using standard collection practices, with or without diversion devices. Within one hour of receipt in the microbiology laboratory, blood culture bottles are manually accessioned in the laboratory information system (LIS)(Epic Beaker, Madison, WI) and placed onto one of four linked automated instruments (Virtuo, BioMeriueX) for a 5 to 10 day incubation protocol, depending on order type. Positive bottles are promptly removed from the instrument, re-scanned into the LIS to generate labels and halt automated “no-growth” LIS updates, Gram-stained, and sub-cultured to appropriate aerobic/anaerobic media, 24 hours, 7 days a week. Within 2 hours of bottles flagging positive and gram stains resulting, verbal reports are given to clinical providers.

During the pre-intervention phase of the study, blood cultures containing Gram-negative bacilli underwent a standardized work-up that included 8 to 36 hours of incubation of primary plates for once daily morning bench reads. Isolated colonies recovered were identified by mass-spectrometry (Vitek MS, BioMeriueX) whereas mixed growth required subculture. All valid identifications (IDs) were manually released to patient charts as they became available. Routine antimicrobial susceptibility testing (AST) was also performed on isolated colonies by Vitek2 using GN-81 cards (BioMeriueX), with supplemental disc diffusion occurring as needed for select confirmatory or supplemental testing. Where Advanced Expert System phenotype and custom rules permitted, automated AST results were finalized in patient charts within 2 to 6 hours of run completion while those requiring additional testing were released once all valid

results became available.

For the post-intervention period, all standardized work-up procedures were exactly as above with the only exception being the introduction of automated ID and AST directly from bottles harboring Gram-negative bacilli using the PhenoTest BC (Accelerate Diagnostics, Tucson, AZ) (Pheno, henceforth). The first positive bottle with pure Gram-negative bacilli (i.e. no evidence of yeast or Gram-positive organism) collected from any unique inpatient encounter qualified for Pheno testing. Once ordered in the LIS, the positive bottle was vortexed and then re-accessed to obtain a 0.5mL aliquot for the Pheno sample vial. All valid Pheno bacterial IDs underwent preliminary auto-verification to the patient chart, and all subsequent valid AST results crossed the interface and were immediately auto-verified. Failed ID or AST Pheno results prompted manual verification of the report with the inclusion of commentary explaining that rapid ID/AST or AST alone would not be forthcoming. In addition to the manufacturer's expert rules for AST reporting on software version 1.4.1.28, customized rules were employed following assay verification and included: (1) any "intermediate" result for ampicillin-sulbactam, ceftazidime, or piperacillin-tazobactam was suppressed, (2) "susceptible" ertapenem results were suppressed for *Serratia marcescens*, and (3) aztreonam "susceptible" results were suppressed for any organism with "resistant" cefepime or ceftriaxone results.

Throughout both phases of the study, quality control testing for all automated and manual ID and AST procedures was performed in accordance with Clinical Laboratory Standards Institute guidelines and verified as acceptable prior to reporting clinical results as outlined by the laboratory's Individualized Quality Control and Quality Management Plans.

2.3. Antimicrobial Stewardship

Once the pathogen identification and the antimicrobial sensitivity information results, the pharmacists will run a report of all the results within the hospital system up to twice a day and will call the team clinician with suggestions regarding the de-escalation of broad-spectrum antibiotics. This occurs on weekdays between 8 AM to 4 PM.

2.4. Retrospective Chart Review Description

This study included a retrospective chart review of patients to record key variables identified to impact the patients' diagnosis and response to treatment. Data was collected using the Epic electronic medical record and included patient demographics, time to de-escalation of antimicrobials, and antimicrobials administered. Demographic data included patient age in years, gender, body mass index (kg/m^2), ethnicity, co-morbidities (e.g. hypertension, diabetes mellitus, autoimmune disorders), use of immunosuppressants (e.g. chemotherapy, disease-modifying anti-rheumatic drugs (DMARDs), steroid use), temperature, mental status, the primary and the secondary source of bacteremia, cardiac

arrest during the hospitalization, admission to the intensive care unit (ICU), in-hospital mortality, 30-day mortality, relapse of the original pathogenic organism, *Clostridioides difficile* infection, and qualitative adverse effects from antimicrobials. Patient demographic information was used to calculate the Pitt bacteremia score (PBS) and Charlson comorbidity index (CCMI). This information was used to ensure balanced cohorts. Missing values were assigned to patients with no available data such as demographics, vital signs, laboratory data, or therapies administered.

2.5. Outcomes

The primary outcomes were the length of stay (LOS), in-hospital mortality, 30-day mortality, empiric antimicrobial costs, and time to de-escalation of therapy which is defined as the amount of time taken to switch from empiric. Secondary outcomes assessed were the duration of empiric antibiotic therapy, adverse reactions to antibiotic therapy such as *Clostridioides difficile* rates, 30-day readmission, and 30-day relapse of the same organism causing bacteremia.

2.6. Statistical Analysis

Statistical analysis was completed using R (R version 4.2.0 2022-04-22ucrt). Demographics, microbiology data, time to de-escalation, and antimicrobial use were tabulated in Microsoft Excel. Univariate analyses were performed on the demographic characteristics for the overall sample, presented by total, and stratified by pre-AXDX and post-AXDX. Chi-square, Fisher's exact tests, and t-tests (normality assessed with Kolmogorov-Smirnov test) were used where appropriate to compare the categorical sample characteristics and numeric variables, between (1) the pre-AXDX cohort, and (2) the post-AXDX cohort. The significance level was set at p-value (p) < .05 for all analyses.

3. Results

Demographic data of pre-AXDX cohort include average age of 60.28 years, 51.38% female, mean BMI of 30.56, mean CCMI of 2.23, mean PBS of 2.35, and mean LOS of 21.19 days. The post-AXDX cohort consisted of an average of 63.66 years old, 51.92% female, mean BMI of 29.11, mean CCMI of 2.99, mean PBS of 2.71 and mean LOS of 15.02. Based on the demographic information such as age, ethnicity, body mass index (BMI), and co-morbidities between the pre-and post-AXDX cohorts, the groups were similar and balanced except for the higher prevalence of dementia, and mild liver disease seen in the post-AXDX cohort and steroid, disease-modifying anti-rheumatic drugs and chemotherapy use and liver disease seen in the pre-AXDX cohort. The 30-day mortality was 21.10% in the pre-AXDX cohort and 17.48% in the post-AXDX cohort ($p = 0.62$). The in-hospital mortality was 14.68% in the pre-AXDX cohort while for post-AXDX, it was 14.42% ($p = 1$). The 30-day relapse of the same organism was 3.03% in the pre-AXDX cohort and 3.85% in the post-AXDX cohort ($p = 1$). Patients were on average on gram-negative empiric therapy for 89 hours

in the pre-AXDX cohort and 73 hours in the post-AXDX. For gram-positive empiric therapy, the pre-AXDX cohort remained on gram-positive empiric therapy for a mean duration of 62 hours and the post-AXDX for a mean duration of 43 hours. The mean TTDeT for the pre-AXDX cohort was 73.90 hours and for the post-AXDX cohort was 43.85 ($p < 0.05$). Pre-AXDX's mean time to speciation and sensitivity (TTSS) was 70.95 hours and 62.92 hours for post-AXDX. The cost of empiric antimicrobial therapy for both gram-positive and gram-negative organisms for the pre-AXDX cohort was \$5128.31 more expensive than the post-AXDX group.

In both groups, the most common source of bacteremia was

from urinary and gastrointestinal etiology. *Escherichia coli* and *Klebsiella pneumoniae* were the most common pathogens seen in both cohorts. Common adverse reactions seen with only the post-AXDX cohorts are rashes, diarrhea, and renal injury. 90-day *Clostridioides difficile* infection was 8.33% in the pre-AXDX cohort and 2.88% in the post-AXDX cohort ($p = 0.15$). The 30-day re-admission unrelated to the initial pathogen was 11.34% in the pre-AXDX cohort and for the post-AXDX cohort, it was 5.77%. The 30-day relapse of the same organism causing bacteremia was 23.71% for the pre-AXDX cohort and 16.35% for the post-AXDX cohort ($p = 0.11$).

Table 1. Patient Characteristics and Comorbidities.

Characteristics	Pre- AXDX n=109	Post- AXDX n=104	p-value
Demographics			
Male	53 (48.62%)	50 (48.08%)	
Female	56 (51.38%)	54 (51.92%)	
Age, mean (standard deviation (SD))	60.28 ± 16.52	63.66 ± 16.82	0.13976
Caucasian	102 (93.58%)	97 (93.27%)	0.61204
Body mass index (BMI), mean (SD)	30.56 ± 10.06	29.11 ± 10.05	0.29251
Top 5 Co-morbidities			
Diabetes mellitus	43 (39.45%)	34 (32.69%)	0.37702
Congestive heart failure	22 (20.18%)	34 (32.69%)	0.0552
Malignancy without metastasis	23 (21.10%)	17 (16.35%)	0.47605
Mild liver disease	4 (3.67%)	27 (25.96%)	0.00001
Chemotherapy use	23 (21.10%)	11 (10.58%)	0.05625
Clinical Factors			
Hypotension	49 (44.95%)	45 (43.27%)	0.91279
Cardiac arrest	8 (7.34%)	9 (8.65%)	0.91961
Mechanical ventilation	24 (22.02%)	21 (20.19%)	0.87411
ICU stay	35 (32.11%)	44 (42.31%)	0.15582
Altered mental status	75 (68.81%)	57 (54.81%)	0.02379
Temperature in °Celsius, mean (SD)	37.97 ± 1.02	37.57 ± 1.00	0.00447
Charlson comorbidity index, mean (SD)	2.23 ± 2.73	2.99 ± 2.56	0.03698
Pitt bacteremia score, mean (SD)	2.35 ± 2.70	2.71 ± 3.28	0.3806

Table 2. Patient Outcomes.

Patient Outcomes	Pre-AXDX n=109	Post-AXDX n=104	p-value
30-day mortality	23 (21.10%)	18 (17.48%)	0.62132
In-hospital mortality	16 (14.68%)	15 (14.42%)	1
Relapse of organism	3 (3.03%)	4 (3.85%)	1
<i>Clostridioides difficile</i> infection	9 (8.33%)	3 (2.88%)	0.1559
Length of stay	21 days	15 days	0.12237
Re-admissions related to bacteremia	24%	16%	0.1118
Mean time to de-escalation/ escalation to appropriate therapy	74 ± 45 hours	44 ± 30 hours	<0.01
Time to susceptibility after culture collection	71.9 ± 29.6 hours	23.7 ± 9.6 hours	< 0.01

Table 3. Top organisms, time to identification, and time to antimicrobial sensitivity.

Pre-AXDX organisms	Pre-AXDX organism count	Pre-AXDX mean ID/AST time (hrs)	Pre-AXDX mean time to de-escalation of antibiotics (hrs)	Post-AXDX organisms	Post-AXDX organism count	Post-AXDX mean ID/AST time (hrs)	Post-AXDX mean time to de-escalation of antibiotics (hrs)
<i>Escherichia coli</i>	46	69.5	66.9	<i>Escherichia coli</i>	50	21.2	38.6
<i>Klebsiella pneumoniae</i>	28	73.3	79.1	<i>Klebsiella pneumoniae</i>	19	19.8	19.8
<i>Pseudomonas aeruginosa</i>	11	72	96.1	<i>Pseudomonas aeruginosa</i>	13	41.6	28.1
<i>Enterobacter cloacae complex</i>	7	88.8	79.7	<i>Enterobacter cloacae complex</i>	7	62	32.2
<i>Proteus mirabilis</i>	6	65.7	64.9	<i>Serratia marcescens</i>	10	41	21.2

Abbreviation- identification (ID); antimicrobial sensitivity testing (AST); hours (hrs)

Table 4. Sources of bacteremia.

Primary bacteremia source	Count (n = 213)
Urinary	91
Gastrointestinal	33
Pulmonary	20
Catheter-associated	16
Unknown	15
Biliary	13
Orthopedic	8
Soft tissue	7
Endovascular	5
Endocarditis	4
Gynecologic	1
Central nervous system	0
Recent surgery	0

Table 5. Costs and duration of empiric coverage.

Pre- AXDX		Post- AXDX	
Median duration of empiric gram-negative (days)	4	Median duration of empiric gram- negative (days)	2
Median duration of empiric gram- positive (days)	2	Median duration of empiric gram- positive (days)	1
Median duration of empiric Anaerobic (days)	3	Median duration of empiric Anaerobic (days)	2
Median time to initial de-escalation (hours)	68	Median time to initial de-escalation (hours)	40
Empiric Gram-negative cost (\$)	\$ 7,924.88	Empiric Gram-negative cost	\$ 3,334.59
Empiric Gram-positive cost (\$)	\$ 765.07	Empiric Gram-positive cost	\$ 227.05
Median time to definitive IV (hours)	84	Median time to definitive IV (hours)	105
Median time to definitive oral antibiotics (hours)	83	Median time to definitive oral antibiotics (hours)	108
Number of patients receiving definitive PO	40	Number of patients receiving definitive oral antibiotics	23
Patients who received definitive oral antibiotics (%)	47	Patients who received definitive oral antibiotics	27

4. Discussion

Based on the results, the clinical outcomes for the pre-AXDX cohort and the post-AXDX cohort were not significantly different, however, there are modest improvements seen in the 30-day mortality, in-hospital mortality, and length of stay. The inability to see statistical significance may be explained by the retrospective approach, suboptimal cohort matching, and lack of power to detect a statistical difference in analyzed measures.

In looking at the literature and our results, there are studies containing similar results that AXDX use does not significantly improve in-hospital mortality and length of stay [9-11]. However, there are several studies with differing findings that showed statistically significant improvements in length of stay and in-hospital mortality [7, 8, 24]. There are several possible reasons for the discrepancies seen in clinical outcomes with AXDX. On average, between both cohorts, our patients were admitted 9 days more than the average length of stay seen in other studies [2-4, 8-10, 17, 23, 30]. This may be due to more co-morbidities, especially with chronic pulmonary disease, obesity, and cardiovascular diseases, as seen in the rural population compared to the urban population of patients [25]. It may also be due to patients delaying seeking medical attention given many of our patients live several hours from our hospital. With the increased burden of chronic illness and lack of immediate medical care, patients may have more complicated hospital courses. Patients that suffer from infections are more likely to have other medical co-morbidities [27]. In the study

completed by Walsh et al., AXDX use statistically impacted the patients that were in the group of those hospitalized for less than 3 days [30]. Since our patients on average, between the two cohorts, were admitted for 18.18 days, clinical impacts of AXDX on 30-day mortality, in-hospital mortality, and length of stay were not statistically significant due to the prolonged hospitalizations leading to more complications and increased risks for subsequent secondary infections.

Based on the two most common gram-negative pathogens, our study matches the results of other studies where *Klebsiella pneumoniae* and *Escherichia coli* are the most common [18, 23]. The rest of the most common pathogens do not match other studies as this may be due to institutional and patient population differences that impact the source of infection as well as the pathogenicity of the microbe. Given that *Pseudomonas*-associated infections tend to have a higher mortality rate, the patients in our study have high CCMI and PBS, and therefore, are much more ill [26].

With the CCMI and PBS, the post-AXDX cohort contained patients that were categorized as more ill. Some other reasons for the differences from the pre-and post-AXDX cohorts may be due to the presence of the COVID-19 pandemic compounded with the fact that our patients are from rural locations. The patient data collected for the post-AXDX cohort was during the peak of the COVID-19 pandemic, and some of the patients may have waited until their illness progressed much further prior to deciding to present to the hospital. In addition, as the largest medical health system in the state, our hospital tends to receive many transfers from smaller, rural hospitals. With the significant patient burden that the COVID-19 pandemic

had on many of our country's hospitals, transfers may have been delayed due to a lack of hospital beds and resources. Patients that would have been transferred to our hospital much sooner may have continued to clinically decompensate while awaiting a bed. This may also explain the differences in liver disease, altered mental status, and CCMI between the pre-AXDX and post-AXDX cohorts. In looking at the literature and prior studies attempting to assess the clinical impact of AXDX, not all studies included CCMI and PBS in the patient demographic information, and the studies that do contain this information have PBS lower than our population of patients [3, 4, 9, 30]. The lower PBS indicates patients with gram-negative bacteremia that are much less ill with less severe infection. In a study done by Bhalodi *et al.*, when patients were broken down by PBS with those containing scores greater than 4 versus scores less than 4. Patients with scores less than 4 and less severe bacteremia had statistically significant improvement in 30-day mortality [4].

With GN-BSI, delayed or inappropriate use of antibiotic therapy can lead to further expenses in the future as antibiotic-resistant infections have been projected to cost the national healthcare system, annually, \$2.2 billion [27]. The rapid de-escalation of antibiotics with AXDX use and the difference of \$5128.31 saved between the pre-and post-AXDX cohorts for both gram-negative and gram-positive empiric antimicrobials will help to decrease health costs as well as delay antimicrobial resistance. Not only did the significant difference in time to de-escalation of antimicrobial therapy impact costs, but it also prevented the development of adverse reactions such as rashes, diarrhea, and renal injury seen in the pre-AXDX cohort. *Clostridioides difficile* rates were also decreased. Given the economic burden of *Clostridioides difficile* infections, with costs as high as \$5.4 billion, though not statistically significant, the reduction of rates seen with AXDX may contribute to the reduction of costs [32].

Our study has some limitations. There were modest improvements seen in the 30-day mortality, in-hospital mortality, and length of stay. These results could be due to the lack of statistical significance may be explained by the retrospective study approach, suboptimal cohort matching, and lack of power to detect a statistical difference in analyzed measures. If the sample sizes were increased to approximately 160 in each group and the trend continues, we would likely see significance in the endpoints.

5. Conclusion

Our results further support prior studies evaluating AXDX and confirms faster ID and AST compared to conventional methods. Patients with severe bacteremia with fewer comorbidities that can prolong hospitalization may benefit more from AXDX use, however, future prospective studies with larger sample sizes are required for this determination. AXDX use leads to significant improvements in the de-

escalation of antimicrobial therapy and decreases in the cost of antibiotic therapy. Further studies are needed to assess if the quicker de-escalation impacts prevalence of MDROs at institutional levels providing additional health benefits and cost-savings.

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