Real-World Impact of the Accelerate PhenoTest® BC Kit on patients with bloodstream infections in IOAS (Improving Outcomes and Antimicrobial Stewardship): A Quasi-Experimental Multicenter Study

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SUMMARY: This real-world quasi-experimental multicenter study found use of the Accelerate PhenoTest® BC Kit testing method for patients with bloodstream infections shortened the time to optimal therapy and time to antimicrobial de-escalation due to faster antimicrobial modifications.

ABSTRACT

Background: Bloodstream infections (BSI) are a leading cause of morbidity and mortality in hospitalized patients. The IOAS (Improving Outcomes and Antimicrobial Stewardship) study seeks to evaluate the impact of the Accelerate PhenoTest® BC Kit (AXDX) on antimicrobial use and clinical outcomes in BSIs.

Methods: This multicenter, quasi-experimental study compared clinical and antimicrobial stewardship metrics, prior to and after implementation of AXDX testing, to evaluate the impact this technology has on patients with BSI. Laboratory and clinical data from hospitalized patients with BSI (excluding contaminants) were compared between two arms, one that underwent testing on AXDX (post-AXDX) and one that underwent alternative organism identification and susceptibility testing (pre-AXDX). The primary outcomes were time to optimal therapy (TTOT) within 96 hours of blood culture positivity and 30-day mortality.

Results: A total of 854 patients with BSI (435 pre-AXDX, 419 post-AXDX) were included. Median TTOT was 17.2 hours shorter in the post-AXDX arm (23.7 hours) compared to the pre-AXDX arm (40.9 hours; $P<0.0001$). Compared with pre-AXDX, median time to first antimicrobial modification (24.2 versus 13.9 hours; $P<0.0001$) and first antimicrobial de-escalation (36.0 versus 27.2 hours; $P=0.0004$) were shorter in the post-AXDX arm. Mortality (8.7% pre-AXDX versus 6.0% post-AXDX), length of stay (7.0 pre-AXDX versus 6.5 days post-AXDX), and adverse drug events were not significantly different between arms. Length of stay was shorter in the post-AXDX arm (5.4 versus 6.4 days; $P=0.03$) among patients with Gram-negative bacteremia.

Conclusions: For BSIs, use of AXDX was associated with significant decreases in TTOT, first antimicrobial modification, and time to antimicrobial de-escalation.

Keywords: bloodstream infections, antimicrobial stewardship, rapid diagnostic tests, antimicrobial susceptibility testing

Introduction

The implementation of rapid diagnostics has been shown to facilitate important antimicrobial interventions and subsequently improve the clinical outcomes of patients with bloodstream infections (BSI) [1,2]. The evaluation of these technologies has predominantly been done as single center quasi-experimental studies, or in a few instances, a more structured study setting such as a randomized controlled trial (RCT) [3,4].

The Accelerate PhenoTest™ BC Kit (AXDX) is the first platform with an assay that provides both early identification (~2 hours) and MIC results (~7 hours) direct from positive blood cultures (PBC) up to 40h faster than conventional methods. The time to result, antimicrobial stewardship (AS) and clinical benefits of implementing AXDX to date has largely been demonstrated with several single center studies [5–9]. A RCT of Gram-negative BSI (GNB) found that AXDX led to faster changes in antimicrobial therapy as compared to conventional testing [4]. The impact amongst hospitals with varying patient populations, laboratory methodologies and clinical practices in a large aggregate data set has not yet been demonstrated. The Improving Outcomes and Antimicrobial Stewardship for Patients with Bloodstream Infection: Accelerate PhenoTest™ BC Kit Registry Study (IOAS), is a multicenter, quasi-experimental study designed to compare clinical and AS metrics, prior to and after the implementation of the AXDX.

METHODS

Study design

IOAS was a multicenter, retrospective, observational study designed to collect data on patients with BSIs who had blood culture testing with organism identification and antimicrobial susceptibility testing (AST) using AXDX in the real-world setting. Data were collected from 5 centers across the United States between April 2017 and November 2019. The study methods have been previously

published in a subgroup analysis of patients with PBC that contained only Gram-positive bacteria (GPB) [10]. Briefly, patients with PBC prior to the implementation of AXDX (pre-AXDX), were compared to patients who had blood culture testing using AXDX (post-AXDX). Hospitalized patients with PBC deemed clinically significant by the participating sites (i.e., not a contaminant) were eligible for inclusion in the IOAS study. Patients who were not admitted to the hospital at the time of PBC, those with a history of PBC in the prior 14 days with the same organism, patients who experienced early mortality (expired within 48 hours of PBC), and patients treated with palliative care and not expected to survive were excluded. Patients were enrolled into the study in an intention-to-treat manner based on whether the PBC met criteria to be run on AXDX, including blood cultures with isolates not included in the AXDX panel of organisms (i.e., 'off-panel'). This study was submitted to and approved by the institutional review board at each participating site. Additional details on the study design and data elements collected can be found in the **Supplementary Methods.**

Microbiological Diagnostics

Details on microbiology workflow, communication of results, and AS program intervention by each hospital can be found in the supplementary material (**Supplementary Methods and Table S1A-S1E**).

Primary Outcome Measures

Primary outcomes were time to optimal therapy (TTOT) in the 96 hours after PBC and 30-day mortality. Optimal therapy was calculated as hours from PBC until first administered dose of optimal antimicrobial therapy (OAT) and was determined by the investigators at each site using institution-specific preferred treatment for the patient based on AST, patient condition and comorbidities, and hospital policy. This *a priori* definition was selected to allow for the assessment of OAT to be made according to each institution's antimicrobial prescribing practices and guidelines, which were not universally defined across study centers. Patients who received OAT prior to PBC and patients who did not receive OAT during the first 96 hours after PBC were excluded from the TTOT analysis, as a

change in the time course of ID/AST reporting is unlikely to impact the timeliness of OAT for these patients. Mortality was defined as death resulting from any cause and based on the patient's status through 30 days after blood culture positivity. Secondary outcome measure definitions can be found in the **Supplementary Methods**.

Statistical Analysis

Baseline comparison of categorical variables between the two arms was performed using Pearson's χ^2 test or Fisher's exact test. Statistical comparisons were performed between study arms with student *t*-test or Mann-Whitney *U* test for continuous variables, where appropriate. Time-to-event antimicrobial-related data were also evaluated by the Kaplan-Meier method and compared using the log-rank test.

A subgroup analysis of subjects with GNB was performed for primary and secondary outcomes, as a similar subgroup analysis of the current study population with GPB has been previously published [10]. Sensitivity analyses of selected patient and infecting organism characteristics were performed for the primary outcomes. All tests were two-tailed, and a *P* value <0.05 was deemed *a priori* to represent statistical significance. Statistical analyses were performed using JMP Version 13.0 (SAS Institute, Inc., Cary, NC).

We determined the sample size for IOAS based on the number of patients needed to have 80% power to conclude that 30-day mortality was different between the two arms. Based on existing literature, it was estimated a pre-AXDX 30-day mortality rate of 16% would require 1000 patients (500 per arm) to detect a relative risk (post-AXDX to pre-AXDX) of 0.6, with a 2-sided α=0.05 test [1,2,11].

RESULTS

Patients

Patient demographics, co-existing conditions, and baseline clinical characteristics were similar between arms except for metastatic tumor being more prevalent in the post-AXDX arm (**Table 1**). Among patients with GNB, the average Pitt Bacteremia Score (PBS) was higher for subjects in the post-AXDX arm (2.2 ± 1.9) than in the pre-AXDX arm (1.7 ± 1.9, *P*=0.007; **Table S1**).

Microbiological characteristics

Of all blood cultures enrolled, 85% had organism(s) which were "on-panel" targets for AXDX (**Table S2**). Arms were similar in distribution of isolated organisms, polymicrobial BSI, and overall frequency of multidrug resistance (**Table 2**). There were more methicillin-resistant *Staphylococcus aureus* (MRSA) and MDR *P. aeruginosa* isolated in the post-AXDX arm and more vancomycin-resistant enterococci (VRE) in the pre-AXDX arm.

The median [IQR] time to PBC from the time of blood culture collection was similar between arms (pre-AXDX 15.3 versus post-AXDX 15.0 hours). Time from PBC to organism identification was 22.3 hours shorter in the post-AXDX than pre-AXDX arm (median 2.5 versus 24.8 hours, *P* <0.0001, **Table S3**). AST was 31.6 hours shorter in the post-AXDX than pre-AXDX arm (median 7.9 versus 39.5 hours, *P*<0.0001).

Antimicrobial measures

TTOT (**Figure 1**) was significantly shorter in the post-AXDX arm (pre-AXDX 40.9 versus post-AXDX 23.7 hours; *P*< 0.0001). TTOT was also improved in the post-AXDX arm when stratifying patients according to severity of illness, intensive care unit (ICU) residence, receipt of vasopressors, and immune status (**Table 3**). However, in those patients with "off-panel" organisms, the median TTOT were not different between pre-AXDX (53.8 hours) and post-AXDX (48.0 hours; *P*=0.47) arms.

The difference in TTOT was slightly greater among the 3 centers (hospital B, C, D in supplementary material) who had expanded AS activities following implementation of AXDX (difference 18.7 hours; pre-AXDX 39.0 [19.7-54.3] versus post-AXDX 20.3 hours [10.0-33.5]; *P*< 0.0001) than the 2 centers (hospital A & E) who did not have expanded AS activities (difference 13.1 hours; pre-AXDX 44.1 [18.8-68.1] versus post-AXDX 31.0 hours [15.1-52.6]; *P*=0.03). The 2 centers (hospital A & B) who implemented AXDX testing for GPB and GNB had a slightly greater difference in TTOT (difference 19.4 hours; pre-AXDX 42.0 [22.8-60.2] versus post-AXDX 23.6 hours [9.9-36.7]; *P*< 0.0001) than the 3 centers that implementing AXDX testing for only GNB (difference 14.8 hours; pre-AXDX 38.6 [17.1-52.9] versus post-AXDX 23.8 hours [10.3-41.6]; *P*= 0.0002).

A total of 415 patients (n=187 pre-AXDX; n=228 post-AXDX) received OAT in the 96 hours after PBC. The proportion of patients receiving OAT prior to PBC (36.7% pre-AXDX; 32.5% post-AXDX) and the proportion of patients who received OAT more than 96 hours after PBC (7.1% pre-AXDX; 4.5% post-AXDX) were not different between arms. The proportion of patients who never received OAT was higher in the pre-AXDX arm versus the post-AXDX arm (13.1% versus 8.6%, *P*=0.03). To assess the impact of excluding patients who did not receive OAT during the 0–96 hour time window after PBC, a sensitivity analysis was performed that assigned a time of 0 hours to patients who received OAT

before PBC and a time of 96 hours to patients who did not received OAT. The difference in TTOT (pre-AXDX 27.7 [0-76] versus post-AXDX 12.4 hours [0-42.5]; difference 15.3 hours; *P*=0.02) was similar. The percentage of patients receiving OAT was significantly higher in the post-AXDX arm at 24 hours (pre-AXDX 48.7% versus post-AXDX 59.9%, *P*=0.001), 48 hours (pre-AXDX 63.5% versus post-AXDX 77.3%, *P*<0.0001), 72 hours (pre-AXDX 74.5% versus post-AXDX 84.0%, *P*=0.0006) and 96 hours (pre-AXDX 79.8% versus post-AXDX 86.9%; *P*=0.005).

Time to first antimicrobial modification (**Figure 2**) occurred 11.3 hours earlier in the post-AXDX arm. Time to first Gram-positive antimicrobial modification, time to first Gram-negative antimicrobial modification, and time to first de-escalation were faster in the post-AXDX arm than the pre-AXDX arm (**Table 4**). Time to first escalation was not different between arms. Antimicrobial modifications were also significantly faster in the post-AXDX arm when restricting the analysis to only subjects with GNB (**Table S4**).

Among patients that were on ineffective empirical antimicrobial therapy, time to effective therapy and TTOT were faster in the post-AXDX arm (**Table 3** and **Table 4**).

Clinical endpoints

There was no statistical difference in 30-day mortality (pre-AXDX 8.7% versus post-AXDX 6.0%; *P* = 0.12) between arms. A sensitivity analysis of patient and infecting organism characteristics that are known to influence mortality was performed because the study did not meet power based on prespecified mortality estimates (**Table 3**). Post-culture length of stay was shorter in the post-AXDX

arm versus the pre-AXDX arm among patients with GNB but did not differ between arms in the overall population (**Table 4**).

DISCUSSION

These real-world data from 5 diverse centers across the US demonstrate the impact a direct from PBC phenotypic assay can have on the management of patients with BSIs. Compared to a historical control arm, several measures of antimicrobial utilization and clinical care were improved following implementation of AXDX. Notably, a 17.2-hour reduction in TTOT, a 10.3-hour shorter time to first antimicrobial modification, and an 8.8-hour reduction in time to first antimicrobial de-escalation. Among patients who did not receive effective empirical antimicrobial therapy, implementation of AXDX facilitated a reduction in the time to effective antimicrobial therapy, an important determinant of outcomes and one of the few of modifiable risk factors for morbidity and mortality [12,13]. Collectively, these findings highlight that the effects of early ID/AST on the care of patients with BSIs were substantial and widespread in this large, pragmatic, multicenter study.

TTOT was significantly shorter in the post-AXDX arm in the overall population and in nearly all subgroups, such as critical illness and immunosuppression that are well-known to influence antimicrobial prescribing practices. Clinicians may be hesitant to de-escalate antimicrobial therapy in many of these populations during the early course of infection due to clinical uncertainty and concern for patient deterioration [3,14,15]. In the current study, the observed reduction in TTOT was independent of organism-related factors, as evident by the ~17-hour difference observed in the overall study population as well as subgroup analyses of GPB and GNB, emphasizing the essential role early AST played in the antimicrobial decision-making process. This point is further demonstrated by the lack of difference in TTOT between arms among patients with “off-panel”

organisms, for which there is no early AST provided in the post-AXDX arm. Thus, the use of the AXDX system was associated with rapid optimization of antimicrobial therapy based on early ID/AST with the impact not confined to any specific patient populations or care settings.

No significant difference in mortality was observed between the study arms despite the post-AXDX arm receiving OAT more quickly. This result may not be unexpected for a few reasons. First, our study did not meet power based on prespecified mortality estimates that were utilized. Specifically, the 30-day mortality rate observed in the pre-AXDX arm was substantially lower (8.7%) than the published literature that was used (~16%) to determine the sample size of this study [1,2,11]. In this study, patients had to survive for ≥48 hours after PBC, which could have led to lower mortality than reported in some of the reference literature. Recent studies that have attempted to understand the impact of AXDX on mortality have also observed pre-AXDX 30-day mortality rates lower than the expected 16%. RAPIDS-GN, a RCT evaluating the clinical impact of AXDX in patients with GNB observed an 8% mortality rate in their pre-AXDX arm [4]. Babowicz et al observed a pre-AXDX 30-day mortality rate of 12.7% among patients with GNB in a single center quasi-experimental study evaluating the implementation of BACT/ALERT® VIRTUO® in conjunction with AXDX [9]. The relatively low rates of MDR organisms and broad-spectrum antimicrobials widely used in septic patients in the studied centers likely resulted in high proportion of patients on effective therapy and therefore a relatively low mortality overall, which is consistent with our observations. Second, the inconsistent mortality findings between RAPIDS-GN (no mortality difference between study arms) and Babowicz et al (reduced hazard ratio for 30-day mortality in post-AXDX) studies highlights the implications that the studied population has on the relationship between early ID/AST and mortality. RAPIDS-GN included all GNB, whereas Babowicz et al included GNB from patients with sepsis. However, neither study had sufficient power to test for a difference in mortality between arms or were not designed to do so. While additional data will be needed to further understand the impact

of early ID/AST on mortality, the current study design, and relatively low rates of antimicrobial resistance (~15%, **Table 2**) prove challenging to accurately assess the outcome of mortality due to population heterogeneity and baseline differences between the arms such as the incidence of metastatic tumor. Such imbalances are highly likely to occur given the goal of this study was to understand the impact of AXDX in a real-world setting rather than the more selected population that is typically enrolled in randomized trials.

Potential insight into the impact of AXDX in getting patients onto faster effective antimicrobials can be observed by focusing on patients initially on ineffective antimicrobial therapy. Kadri et al evaluated the impact of inappropriate empiric therapy based on discordant *in vitro* susceptibilities in ~21,000 patients with BSIs and demonstrated a strong correlation between ineffective therapy and mortality (OR 1.46 [95% CI 1.43-2.40; p<0.0001])[12]. Twenty-four percent of patients (n=203) in the current study received initial ineffective therapy. Within this subgroup, a mortality rate of 14.4% was observed in the pre-AXDX arm compared to 8% in the post-AXDX arm. This difference may be attributed to the shortened duration of ineffective therapy as well as the 24-hour improvement in OAT. While statistical significance was not observed for mortality within this subgroup (*P*=0.14), the relative difference between arms is likely of clinical significance.

While overall secondary clinical endpoints were not statistically different, the impact of early ID/AST results on the care of patients with BSIs were evident in subgroup analyses. There was a one-day reduction in LOS observed for patients with GNB in the post-AXDX arm, further supporting the LOS savings that has been observed in this population among other single center studies [5–7].

While the main intervention studied in these data was the use of AXDX, it is important to note that all sites had AS programs in place which have been previously demonstrated to greatly enhance the impact of diagnostics [3,16,17]. At some of the study sites (**Table S1**), additional AS processes were implemented in the post-AXDX arm, including use of real-time notification of AXDX results in some instances, which resulted in a slightly greater difference in TTOT between arms than study sites which did not implemented additional AS processes. While the implications of this slightly greater difference in TTOT are unknown, Dare et al found that the addition of real-time notification did not further improve study outcomes beyond those observed with implementation of AXDX with routine monitoring of PBC and intervention [7].

A few strengths and limitations of these data should be noted. First, TTOT was investigator defined at each site by a practicing clinical pharmacist or infectious diseases physician through manual evaluation of each antimicrobial to make the assessment of OAT. This allows for varying clinical practices as there is no universally accepted definition for OAT that crosses all patient populations. Similarly, the clinical laboratory methods utilized for processing PBC differed from site to site in the pre-AXDX arm including the use of various instruments and workflows. The benefits of this approach include the ability to assess varying blood culture practices and diagnostic assays, however this also introduces additional heterogeneity. The patient populations at the sites likely varied as institutions ranged from large community and/or academic medical centers to specialty care institutions. While this can be considered a strength, it did result in some imbalances between groups in terms of patient and isolate characteristics, such as the considerable differences in rates of certain MDR organisms which could have implications on some of the study endpoints. Randomization as part of the study design would have likely helped to alleviate some of these imbalances between the two arms making the quasi-experimental design of this study a limitation. The current study included all PBC that would have received AXDX testing and did not exclude “off-

panel" organisms, which is likely a more real-world representation of workflow processes and overall patient impact. This allowed us to assess the impact of AXDX across a large patient population, but also contributed to the large amount of variability that was observed as well.

This multicenter, real-world study suggests early ID/AST via AXDX has a significant impact on optimizing antimicrobial utilization and outcomes for patients with BSIs. While challenging to demonstrate definitively, the value of early antimicrobial optimization is likely associated with widespread patient and societal benefits such as limiting the emergence of antimicrobial resistance and reduced harm from unnecessary antimicrobial exposures. As antimicrobial resistance rates increase across society and the new antimicrobial pipeline atrophies, the rapid institution of optimal antimicrobial therapy to patients with serious bacterial infections is likely to become increasingly impactful.

NOTES

Funding

This work was supported by Accelerate Diagnostics, Inc. (research grant support for current study to each participating institution).

Potential Conflicts

A.A.B., S.H.M., and R.M.H. are current/former employees of Accelerate Diagnostics, Inc. and were involved in the design, execution, analysis and reporting of the research. M.A.M and T.L.W. reports receiving consulting fees and/or honoraria from Accelerate Diagnostics, outside the submitted work. R.M.H reports receiving consulting fees from Accelerate Diagnostics and Specific Diagnostics, outside the submitted work and has stock or stock options from Accelerate Diagnostics. D.R.C reports Speaker's Bureau fees from Merck, outside the submitted work. B.F. reports grants from Cepheid and consulting fees from Peak Diagnostics, outside the submitted work. A.A.B. and S.H.M. report stock or stock options from Accelerate Diagnostics, Inc. M.A.M. reports participation on a Data Safety Monitoring Board or Advisory Board for Accelerate Diagnostics, Inc.

All other none to declare

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Table 1. Demographics and baseline characteristics of patients

	Pre-AXDX (*n*=435)	Post-AXDX (*n*=419)	*P* value
Demographics			
male sex	226 (51.2)	224 (53.5)	0.66
age, years, mean ± SD	58.2 ± 20.1	59.1 ± 21.1	0.22
age <18 years old	16 (3.7)	24 (5.7)	
Co-existing conditions			
Charlson comorbidity score, mean ± SD	5.1 ± 3.4	5.3 ± 3.6	0.46
malignancy	179 (41.1)	168 (40.0)	0.75
leukemia, lymphoma, local tumor	144 (33.1)	115 (27.5)	
metastatic tumor	35 (8.1)	53 (12.7)	**0.03**
diabetes mellitus	142 (32.6)	136 (32.5)	0.89
chronic kidney disease	107 (24.6)	92 (22.0)	0.36
chronic liver disease	62 (14.3)	68 (16.4)	0.33
Clinical characteristics at blood culture positivity			
source of bacteremia[a]			0.19
bone/joint	14 (3.2)	18 (4.3)	
cardiovascular	13 (3.0)	11 (2.6)	
central venous catheter	64 (14.7)	45 (10.7)	
intra-abdominal	70 (16.1)	87 (20.8)	
respiratory	23 (5.3)	12 (2.9)	
skin/soft tissue	16 (3.7)	7 (1.7)	
urinary	94 (21.6)	96 (22.9)	
other	16 (3.7)	7 (1.7)	
unidentified	121 (27.8)	119 (28.4)	
immunosuppressant use[b]	135 (31.0)	128 (30.6)	0.88
concurrent infection requiring antimicrobial therapy[c]	75 (17.2)	76 (18.1)	0.73
acquisition type			
community acquired[d]	314 (72.2)	303 (72.3)	0.97
ICU residence	126 (29.0)	107 (25.5)	0.26
Pitt bacteremia score[e]	2.0 ± 2.3	2.2 ± 2.0	0.28
quick SOFA (qSOFA) score[e]	0.78 ± 0.72	0.72 ± 0.71	0.24
serum creatinine, mg/dL[e] ± SD	1.6 ± 1.5	1.6 ± 1.6	0.97
requiring mechanical ventilation	61 (14.0)	62 (14.8)	0.74
hypotension (systolic blood pressure <90 mm Hg)	103 (23.7)	113 (27.0)	0.26
required IV vasopressors	73 (16.8)	59 (14.1)	0.28

Data are presented as *n* (%) of patients, unless specified otherwise.

Significant differences are highlighted in bold.

[a] Source of bacteremia: (i) for a bloodstream infection to be determined secondary to another site of infection, at least one organism from the blood specimen must match an organism identified from the site-specific infection; (ii) if there is not another site of infection with organism growth, a clinician may determine the likely source of the bacteremia based on their clinical judgement; and (iii) unidentified: unknown or no clear source of bacteria.

[b] Immunosuppression included any of the following: (i) active systemic chemotherapy, tacrolimus, mycophenolate mofetil, azathioprine, cyclosporine (or equivalent therapy), for more than 7 days OR a systemic steroid for more than 10 days in the previous month; or (ii) absolute neutrophil count <1500.

[c] A patient was classified as with a concurrent infection when a culture from the concomitant infection site grew at least one organism that was not isolated from blood or had a suspected infection that required additional antimicrobial therapy.

[d] Occurred prior to hospitalization or within ≤2 days of hospital admission.

[e] Evaluated for patients ≥18 years of age

Table 2. Blood culture organisms

	Pre-AXDX (*n*=435)	Post-AXDX (*n*=419)
Total organisms isolated	487	430
Gram-positive, by isolate	155 (31.8)	143 (33.3)
CoNS	45 (9.2)	39 (9.1)
S. aureus	36 (7.4)	45 (10.5)
Enterococcus spp.	27 (5.5)	18 (4.2)
Streptococcus spp.	32 (6.6)	35 (8.1)
Other, Gram-positive	15 (3.1)	6 (1.4)
Gram-negative, by isolate	328 (67.4)	276 (64.2)
Acinetobacter baumannii	2 (0.4)	1 (0.2)
Citrobacter spp.	5 (1.0)	4 (0.9)
Escherichia coli	140 (28.8)	123 (28.6)
Enterobacter spp.	21 (4.3)	22 (5.1)
Klebsiella spp.	53 (10.9)	53 (12.3)
Proteus spp.	10 (2.1)	9 (2.1)
Pseudomonas aeruginosa	33 (6.8)	27 (6.3)
Serratia marcescens	13 (2.7)	6 (1.4)
Other, Gram-negative	51 (10.5)	31 (7.2)
Yeast, by isolate	4 (0.8)	11 (2.6)
AXDX off-panel organism isolated	86 (17.7)	62 (14.4)
Polymicrobial blood culture	58 (13.3)	47 (11.2)
Proportion of blood cultures with all organisms on AXDX ID/AST panel	360/435 (82.8)	365/419 (87.1)
Multidrug-resistance (MDR) in blood culture isolates[a]	54 (12.4)	69 (16.5)
methicillin-resistant *Staphylococcus aureus*	9/36 (25.0)	20/45 (44.4)
vancomycin-resistant enterococci	7/27 (25.9)	2/18 (11.1)
Extended-spectrum cephalosporin-resistant Enterobacterales	36/242 (14.9)	35/217 (16.1)
MDR *Acinetobacter* spp.	1/2	0/1
MDR *Pseudomonas aeruginosa*	1/33 (0.5)	11/27 (40.7)

Data are presented as *n* (%) of patients, unless specified otherwise.

[a]The isolation of a multidrug-resistant organism includes vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, extended-spectrum cephalosporin-resistant Enterobacterales, and *Pseudomonas aeruginosa* and *Acinetobacter* species non-susceptible to at least 1 agent in ≥3 antimicrobial categories as described by Magiorakos *et al*.[18]

a. Extended-spectrum cephalosporin-resistant Enterobacterales will be defined as the as intermediate or resistant to a 3rd-generation cephalosporin.

b. Carbapenem-resistant Enterobacterales will be defined as intermediate or resistant to imipenem, doripenem, ertapenem (R only), or meropenem. If the sensitivity test indicated the specimen was resistant to any of those medications the specimen was categorized as “Carbapenem not susceptible”

Other organisms in the pre-AXDX arm:

Gram-positive: *Abiotrophia defectiva*, *Actinomyces odontolyticus*, *Anaerococcus prevotii*, *Bacillus* spp., *Clostridium* spp. (3), *Corynebacterium* spp. (3), *Finegoldia magna*, *Nocardia farcinica*, *Paenibacillus* spp., *Peptoniphilus harei*, *Peptostreptococcus* spp.

Gram-negative: *Acinetobacter* spp. [non-baumannii] (4), *Aeromonas* spp. (2), *Alcaligenes xylosoxidans*, Anaerobic Gram-negative rod [Unable to further identify], *Bacteroides* spp. (7), *Elizabethkingae meningiosepticum* group, *Flavobacterium meningosepticum* (2), *Fusobacterium* spp. (4), *Haemophilus* spp. (4), *Moraxella* spp. (2), *Morganella morganii* (3), *Pantoea* spp. (2), *Prevotella* spp. (2), *Pseudomonas* spp. [non-aeruginosa] (2), *Salmonella* spp. (4), *Sphingomonas paucimobilis* (1); *Stenotrophomonas maltophilia* (6), *Veillonella* spp. (2), *Vibrio* spp.

Other organisms in the post-AXDX arm:

Gram-positive: *Bacillus* spp. (3), *Corynebacterium* spp., *Finegoldia magna*, *Lactobacillus* spp.

Gram-negative: *Achromobacter xyloxidans*, *Bacteroides* spp. (12), *Chryseobacterium indologenes*, *Fusobacterium* spp. (2), *Haemophilus* spp. (2), *Morganella morganii*, *Pantoea* spp. (2), *Pasteurella multocida*, *Prevotella* spp. (2), *Pseudomonas* spp. [non-aeruginosa], *Salmonella* spp. (3), *Sphingomonas paucimobilis*, *Stenotrophomonas maltophilia* (2)

Table 3. Time to optimal therapy and 30-day mortality by subgroup

	Time to optimal therapy			30-day mortality		
	Pre-AXDX (*n*=187)	Post-AXDX (*n*=228)	*P* value	Pre-AXDX (*n*=435)	Post-AXDX (*n*=419)	*P* value
All	40.9 (19.4-58.4)	23.7 (10.3-37.8)	**<.0001**	38 (8.7)	25 (6.0)	0.12
Pitt bacteremia score ≥4	40.9 (19.3-49.8)	23.0 (10.2-35.9)	**0.01**	17 (22.7)	16 (18.6)	0.53
Pitt bacteremia score <4	40.5 (19.7-59.6)	24.7 (10.3-38.3)	**<.0001**	21 (5.8)	9 (2.7)	**0.04**
In ICU at time of blood culture positivity	41.4 (19.8-58.3)	24.2 (11.1-34.0)	**0.0005**	27 (16.8)	16 (11.4)	0.18
Not in ICU at time of blood culture positivity	39.2 (18.8-58.5)	23.4 (10.2-41.7)	**<.0001**	11 (4.0)	9 (3.2)	0.62
Immunosuppressed	42.8 (20.7-68.0)	25.2 (10.1-45.3)	**0.002**	14 (10.4)	11 (8.6)	0.62
Not immunosuppressed	40.1 (18.8-54.7)	23.0 (10.3-34.8)	**<.0001**	24 (8.0)	14 (4.8)	0.11
Receiving IV vasopressors	37.6 (14.4-55.0)	20.8 (11.1-42.3)	0.29	17 (23.3)	10 (17.0)	0.37
Not receiving IV vasopressors	40.9 (23.1-58.5)	24.0 (10.2-36.6)	**<.0001**	21 (5.8)	15 (4.2)	0.31
Concurrent infection requiring antimicrobial therapy	38.2 (15.2-50.2)	19 (6.7-37.1)	0.11	6 (8.0)	4 (5.3)	0.53
No concurrent infection requiring antimicrobial therapy	41.7 (22.8-61.3)	24.4 (10.7-38.2)	**<.0001**	32 (8.9)	21 (6.1)	0.20
On-panel organism(s)	39.2 (18.0-55.5)	21.5 (10.2-35.4)	**<.0001**	28 (7.8)	22 (6.0)	0.35
Off-panel organism(s)	53.8 (31.3-71.5)	48.0 (33.1-64.1)	0.47	10 (13.3)	3 (5.6)	0.13
Monomicrobial culture result	40.9 (22.7-58.4)	23.8 (10.3-36.7)	**<.0001**	31 (8.2)	22 (5.9)	0.22
Polymicrobial culture result	43.0 (8.6-58.0)	17.9 (6.0-60.2)	0.47	7 (12.1)	3 (6.4)	0.32

Effective therapy at time of blood culture positivity	42.5 (28.5-59.6)	27.7 (14.5-27.7)	**<.0001**	24 (7.1)	16 (5.3)	0.33
Ineffective therapy at time of blood culture positivity	36.9 (13.1-54.3)	12.4 (5.7-31.2)	**<.0001**	13 (14.4)	9 (8.0)	0.14

Data points were evaluated at 96 h after blood culture positivity and are reported as median (IQR), unless specified otherwise.

Number of observations for each variable are included as (*n*=).

Significant differences are highlighted in bold.

Table 4. Antimicrobial modifications and Clinical outcomes

	All[a]			Gram-negative[b]		
	Pre-AXDX	Post-AXDX	*P* value	Pre-AXDX	Post-AXDX	*P* value
Antimicrobial modifications						
Time to first antimicrobial modification[c]	24.2 (7.3-46.2)	13.9 (5.0-31.1)	**<.0001**	22.8 (7.0-45.3)	13.6 (5.8-30.9)	**0.01**
Time to first Gram-positive antimicrobial modification[d]	30.1 (11.2-52.8)	18.3 (6.7-41.8)	**0.0013**	28.1 (10.5-51.7)	18.6 (9.4-42.1)	0.11
Time to first Gram-negative antimicrobial modification[e]	34.6 (9.2-53.4)	18.6 (8.2-36.8)	**<.0001**	30.2 (7.6-52.8)	16.7 (8.6-35.2)	**0.003**
Time to first antimicrobial escalation[f]	9.5 (3.4-28.9)	9.0 (3.7-18.4)	0.22	9.5 (3.7-31.6)	9.6 (3.9-18.4)	0.44
Time to first antimicrobial de-escalation[g]	36.0 (17.1-54.5)	27.2 (13.5-43.6)	**0.0004**	34.5 (16.6-52.8)	25.4 (12.0-42.5)	**0.003**
Time to effective therapy[h]	13.3 (3.1-35.9)	6.7 (3.1-16.2)	**0.02**	13.7 (3.3-38.1)	10.0 (3.6-18.6)	0.10
Clinical outcomes						
30-day mortality	38 (8.7)	25 (6.0)	0.12	25 (8.3)	19 (6.7)	0.47
Post-blood culture length of stay, days, median (IQR)	7.0 (4.0-12.4)	6.5 (3.7-12.0)	0.43	6.4 (3.7-11.7)	5.4 (3.4-9.7)	**0.03**
Acute kidney injury (≥18 years old)	92 (23.2)	78 (21.1)	0.49	64 (22.7)	57 (21.6)	0.76
14-day RRT	15 (3.5)	9 (2.2)	0.25	10 (3.3)	5 (1.8)	0.24
30-day CDI (day 3-30)	3 (0.7)	4 (1.0)	0.67	0	1 (0.4)	0.48
Acquisition of new MDROs within 30 days	22 (5.1)	15 (3.6)	0.29	17 (5.7)	9 (3.2)	0.15
Readmission within 30 days	76 (19.4)	91 (23.8)	0.14	52 (18.6)	51 (19.4)	0.82
Readmission within 30 days from bacteremia	15 (3.8)	16 (4.2)	0.68	7 (2.5)	11 (4.2)	0.54

All data are reported as *n* (%), unless specified otherwise. Significant differences are highlighted in bold.

[a] n = 435 for pre-AXDX and 419 for post-AXDX, unless specified otherwise

[b] n = 301 for pre-AXDX and 282 for post-AXDX, unless specified otherwise

[c] Evaluated among patients who had an antimicrobial modification during the first 96 h after blood culture positivity (n=693)

[d] Evaluated among patients who had a Gram-positive antimicrobial modification during the first 96 h after blood culture positivity (n=383)

[e] Evaluated among patients who had a Gram-negative antimicrobial modification during the first 96 h after blood culture positivity (n=578)

[f] Evaluated among patients who had an antimicrobial escalation during the first 96 h after blood culture positivity (n=307)

[g] Evaluated among patients who had an antimicrobial de-escalation during the first 96 h after blood culture positivity (n=581)

[h] Evaluated among patients on ineffective therapy at time of blood culture positivity (n=203)

LTACH, long-term acute care hospital; RRT, renal replacement therapy; SNF, skilled nursing facility.

The isolation of an MDR organism includes vancomycin-resistant enterococci, MRSA, extended-spectrum cephalosporin-resistant Enterobacterales and *Pseudomonas aeruginosa* and *Acinetobacter* species non-susceptible to at least 1 agent in ≥3 antimicrobial categories as described by Magiorakos *et al*.[18] (i) Extended-spectrum cephalosporin-resistant Enterobacterales will be defined as the as intermediate or resistant to a third-generation cephalosporin. (ii) Carbapenem-resistant Enterobacterales will be defined as intermediate or resistant to imipenem, doripenem, ertapenem (R only) or meropenem. If the susceptibility test indicated the specimen was resistant to any of those medications the specimen was categorized as 'carbapenem non-susceptible'.

FIGURE LEGENDS

Figure 1. Kaplan–Meier analysis of the time from blood culture positivity to optimal antimicrobial therapy.

Log-rank *P*< 0.0001.

Figure 2. Kaplan–Meier analysis of the time from blood culture positivity to first antimicrobial modification.

Log-rank *P*< 0.0001.

Figure 1

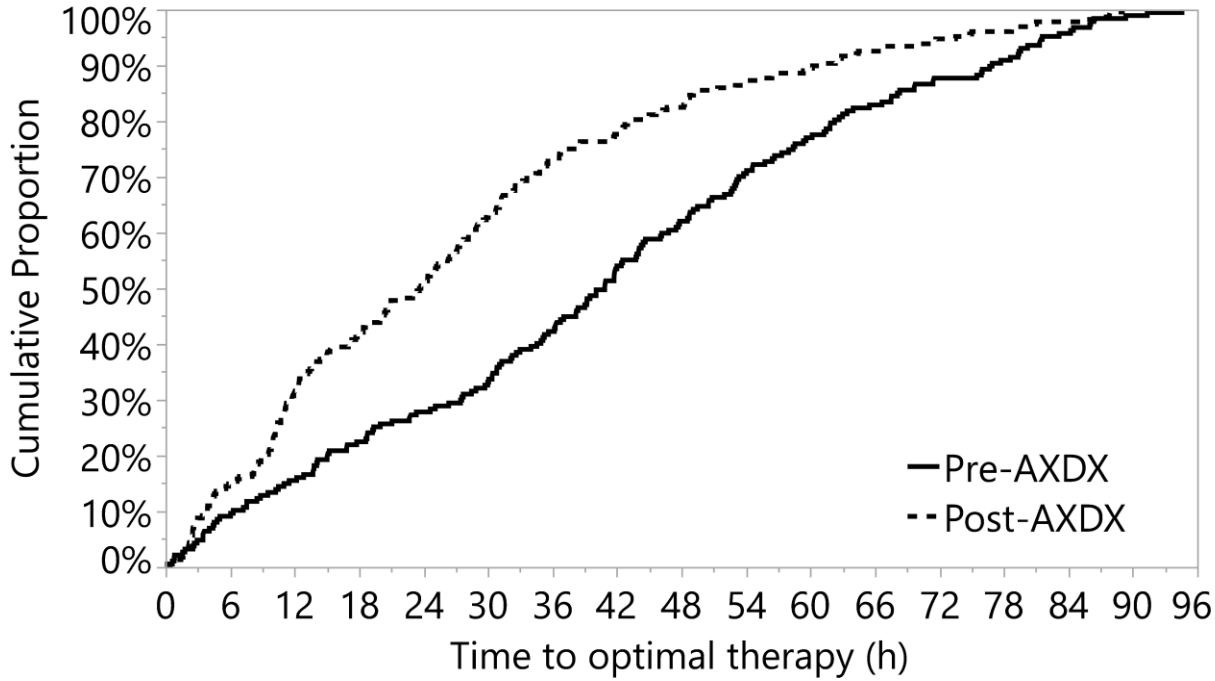

Figure 2