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Real-World Impact of the Accelerate PhenoTest BC Kit on Patients With Bloodstream Infections in the Improving Outcomes and Antimicrobial Stewardship Study: A Quasiexperimental Multicenter Study

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Background. Bloodstream infections (BSIs) are a leading cause of morbidity and mortality. The 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, quasiexperimental study compared clinical and antimicrobial stewardship metrics, prior to and after implementation of AXDX, to evaluate the impact this technology has on patients with BSIs. Laboratory and clinical data from hospitalized patients with BSIs (excluding contaminants) were compared between 2 arms, 1 that underwent testing on AXDX (post-AXDX) and 1 that underwent alternative organism identification and susceptibility testing (pre-AXDX). The primary outcomes were time to optimal therapy (TTOT) and 30-day mortality.

Results. A total of 854 patients with BSIs (435 pre-AXDX, 419 post-AXDX) were included. Median TTOT was 17.2 hours shorter in the post-AXDX arm (23.7 hours) compared with the pre-AXDX arm (40.9 hours; $P < .0001$). Compared with pre-AXDX, median time to first antimicrobial modification (24.2 vs 13.9 hours; $P < .0001$) and first antimicrobial deescalation (36.0 vs 27.2 hours; $P = .0004$) were shorter in the post-AXDX arm. Mortality (8.7% pre-AXDX vs 6.0% post-AXDX), length of stay (7.0 pre-AXDX vs 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 vs 6.4 days; $P = .03$) 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 deescalation.

Keywords. bloodstream infections; antimicrobial stewardship; rapid diagnostic tests; antimicrobial susceptibility testing.

The implementation of rapid diagnostics has been shown to facilitate important antimicrobial interventions and subsequently improve the clinical outcomes of patients with bloodstream infections (BSIs) [1, 2]. The evaluation of these technologies has predominantly been done as single-center, quasiexperimental 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 (approximately 2 hours) and minimum inhibitory concentration results (approximately 7 hours) direct from positive blood cultures (PBCs) up to 40 hours faster than conventional methods. The time to result, antimicrobial stewardship (AS), and clinical benefits of implementing AXDX to date have largely been demonstrated with several single-center studies [5–9]. A RCT of gram-negative BSI (GNB) found that AXDX led to faster

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changes in antimicrobial therapy compared with conventional testing [4]. The impact among hospitals with varying patient populations, laboratory methodologies, and clinical practices in a large aggregate dataset 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, quasiexperimental study designed to compare clinical and AS metrics prior to and after implementation of the AXDX.

METHODS

Study Design

IOAS is a multicenter, retrospective, observational study designed to collect data on patients with BSIs who had blood culture testing with organism identification (ID) and antimicrobial susceptibility testing (AST) using AXDX in a 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 PBCs that contained only gram-positive bacteria (GPB) [10]. Briefly, patients with PBCs prior to the implementation of AXDX (pre-AXDX) were compared to patients who had blood culture testing using AXDX (post-AXDX). Hospitalized patients with PBCs deemed clinically significant by the participating sites (ie, 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 (ie, "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 Methods and Supplementary Table 1A–1E.

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 Analyses

Baseline comparison of categorical variables between the 2 arms was performed using the Pearson χ^2 test or Fisher exact test. Statistical comparisons were performed between study arms with the Student *t* test or Mann-Whitney *U* test for continuous variables, where appropriate. Time-to-event antimicrobial-related data were also evaluated using the Kaplan-Meier method and compared using the log-rank test.

A subgroup analysis of patients 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 2-tailed, and a P value < .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 2 arms. Based on existing literature, it was estimated that 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 $\alpha = 0.05$ test [1, 2, 11].

RESULTS

Patients

Patient demographics, coexisting 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 was higher for patients in the post-AXDX arm (2.2 ± 1.9) than in the pre-AXDX arm (1.7 ± 1.9; $P = .007$; Supplementary Table 1).

Microbiological Characteristics

Of all blood cultures enrolled, 85% had organism(s) that were "on-panel" targets for AXDX (Supplementary Table 2). Arms were similar in distribution of isolated organisms, polymicrobial

Table 1. Demographics and Baseline Patient Characteristics

Demographics and Characteristics	Pre-AXDX (n = 435)	Post-AXDX (n = 419)	*P* Value
Demographics			
Male sex	226 (51.2)	224 (53.5)	.66
Age, mean ± SD, years	58.2 ± 20.1	59.1 ± 21.1	.22
Age <18 years	16 (3.7)	24 (5.7)	
Coexisting conditions			
Charlson comorbidity score, mean ± SD	5.1 ± 3.4	5.3 ± 3.6	.46
Malignancy	179 (41.1)	168 (40.0)	.75
Leukemia, lymphoma, local tumor	144 (33.1)	115 (27.5)	
Metastatic tumor	35 (8.1)	53 (12.7)	**.03**
Diabetes mellitus	142 (32.6)	136 (32.5)	.89
Chronic kidney disease	107 (24.6)	92 (22.0)	.36
Chronic liver disease	62 (14.3)	68 (16.4)	.33
Clinical characteristics at blood culture positivity			
Source of bacteremia[a]			.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)	
Intraabdominal	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)	.88
Concurrent infection requiring antimicrobial therapy[c]	75 (17.2)	76 (18.1)	.73
Acquisition type			
Community acquired[d]	314 (72.2)	303 (72.3)	.97
Intensive care unit residence	126 (29.0)	107 (25.5)	.26
Pitt bacteremia score[e]	2.0 ± 2.3	2.2 ± 2.0	.28
Quick sequential organ failure assessment score[e]	0.78 ± 0.72	0.72 ± 0.71	.24
Serum creatinine, mg/dL[e] ± SD	1.6 ± 1.5	1.6 ± 1.6	.97
Requiring mechanical ventilation	61 (14.0)	62 (14.8)	.74
Hypotension (systolic blood pressure <90 mm Hg)	103 (23.7)	113 (27.0)	.26
Required intravenous vasopressors	73 (16.8)	59 (14.1)	.28

Data are presented as n (%) of patients, unless specified otherwise. Significant differences are highlighted in bold.

Abbreviations: AXDX, Accelerate PhenoTest BC Kit; SD, standard deviation.

[a]Source of bacteremia: (i) for a bloodstream infection to be determined secondary to another site of infection, at least 1 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 judgment; and (iii) unidentified: unknown or no clear source of bacteria.

[b]Immunosuppression included any of the following: 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 absolute neutrophil count <1500.

[c]A patient was classified as having a concurrent infection when a culture from the concomitant infection site grew at least 1 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 aged ≥18 years.

BSI, and overall frequency of multidrug resistance (Table 2). There were more methicillin-resistant *Staphylococcus aureus* and multidrug-resistance (MDR) *Pseudomonas aeruginosa* isolated in the post-AXDX arm and more vancomycin-resistant enterococci in the pre-AXDX arm.

The median (interquartile range) time to PBC from the time of blood culture collection was similar between arms (pre-AXDX 15.3 vs post-AXDX 15.0 hours). Time from PBC to organism identification was 22.3 hours shorter in the post-AXDX arm than in the pre-AXDX arm (median 2.5 vs 24.8 hours; $P < .0001$; Supplementary Table 3). AST was 31.6 hours shorter in the post-AXDX arm than in the pre-AXDX arm (median 7.9 vs 39.5 hours; $P < .0001$).

Antimicrobial Measures

TTOT (Figure 1) was significantly shorter in the post-AXDX arm (pre-AXDX 40.9 vs post-AXDX 23.7 hours; $P < .0001$). TTOT was also improved in the post-AXDX arm when patients were stratified according to severity of illness, intensive care unit residence, receipt of vasopressors, and immune status (Table 3). However, in those patients with off-panel organisms, the median TTOT were not different between

Table 2. Blood Culture Organisms

Organism	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)
Staphylococcus 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 identification/ antimicrobial susceptibility testing panel	360/435 (82.8)	365/419 (87.1)
MDR in blood culture isolates[a]	54(12.4)	69(16.5)
Methicillin-resistant *S. 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 *P. aeruginosa*	1/33 (0.5)	11/27 (40.7)

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

Abbreviations: AXDX, Accelerate PhenoTest BC Kit; CoNS, coagulase-negative staphylococci; MDR, multidrug resistant.

[a]The isolation of a MDR organism includes vancomycin-resistant enterococci, methicillin-resistant *S. aureus*, extended-spectrum cephalosporin-resistant Enterobacterales, and *P. aeruginosa* and *Acinetobacter* species nonsusceptible to at least 1 agent in ≥3 antimicrobial categories as described by Magiorakos et al [18]. (i) Extended-spectrum cephalosporin-resistant Enterobacterales defined as intermediate or resistant to a third-generation cephalosporin. (ii) Carbapenem-resistant Enterobacterales 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 nonsusceptible."

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).

pre-AXDX (53.8 hours) and post-AXDX (48.0 hours; $P = .47$) arms.

The difference in TTOT was slightly greater among the 3 centers (hospitals B, C, and D in the Supplementary Material) that had expanded AS activities following implementation of AXDX (difference, 18.7 hours; pre-AXDX 39.0 [19.7–54.3] vs post-AXDX 20.3 hours [10.0–33.5]; $P < .0001$) than the 2 centers (hospitals A and E) that did not have expanded AS activities (difference, 13.1 hours; pre-AXDX 44.1 [18.8–68.1] vs post-AXDX 31.0 hours [15.1–52.6]; $P = .03$). The 2 centers (hospitals A and B) that 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] vs post-AXDX 23.6 hours [9.9–36.7]; $P < .0001$) than the 3 centers that implemented AXDX testing for only GNB (difference, 14.8 hours; pre-AXDX 38.6 [17.1–52.9] vs post-AXDX 23.8 hours [10.3–41.6]; $P = .0002$).

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 who received 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 vs the post-AXDX arm (13.1% vs 8.6%; $P = .03$). 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

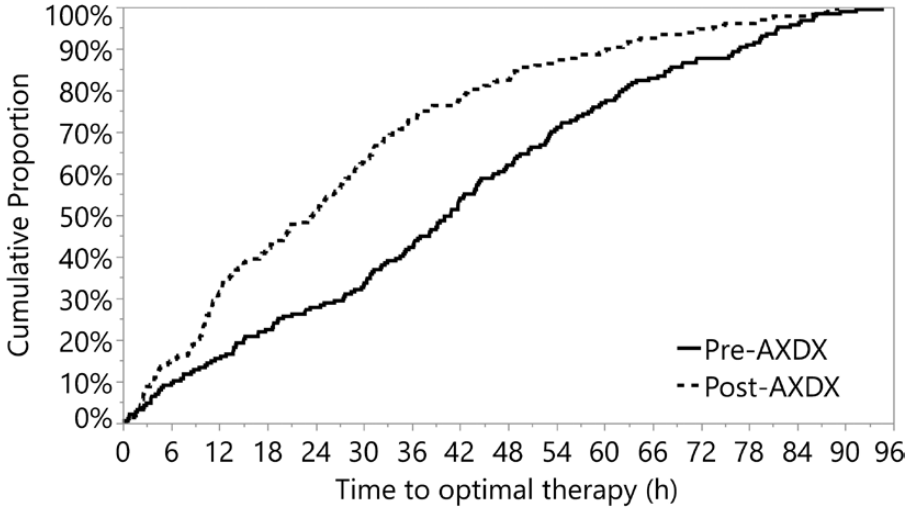

Figure 1. Kaplan-Meier analysis of the time from blood culture positivity to optimal antimicrobial therapy. Log-rank $P < .0001$. Abbreviation: AXDX, Accelerate PhenoTest BC Kit.

of 96 hours to patients who did not received OAT. The difference in TTOT (pre-AXDX 27.7 [0–76] vs post-AXDX 12.4 hours [0–42.5]; difference, 15.3 hours; $P = .02$) was similar. The percentage of patients who received OAT was significantly higher in the post-AXDX arm at 24 hours (pre-AXDX 48.7% vs post-AXDX 59.9%; $P = .001$), 48 hours (pre-AXDX 63.5% vs post-AXDX 77.3%; $P < .0001$), 72 hours (pre-AXDX 74.5% vs post-AXDX 84.0%; $P = .0006$), and 96 hours (pre-AXDX 79.8% vs post-AXDX 86.9%; $P = .005$).

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 deescalation were faster in the post-AXDX arm than in 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 the analysis was restricted to only patients with GNB (Supplementary Table 4).

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

Clinical End Points

There was no statistical difference in 30-day mortality (pre-AXDX 8.7% vs post-AXDX 6.0%; $P = .12$) 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 (LOS) was shorter in the post-AXDX arm vs 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 United States demonstrate the impact a direct, from-PBC phenotypic assay can have on the management of patients with BSIs. Compared with 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 deescalation. 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 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 deescalate 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 approximately 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

Table 3. Time to Optimal Therapy and 30-Day Mortality by Subgroup

	Time to Optimal Therapy			30-Day Mortality		
Patients	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)	.12
Pitt bacteremia score ≥4	40.9 (19.3–49.8)	23.0 (10.2–35.9)	**.01**	17 (22.7)	16 (18.6)	.53
Pitt bacteremia score <4	40.5 (19.7–59.6)	24.7 (10.3–38.3)	**<.0001**	21 (5.8)	9 (2.7)	**.04**
In ICU at time of blood culture positivity	41.4 (19.8–58.3)	24.2 (11.1–34.0)	**.0005**	27 (16.8)	16 (11.4)	.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)	.62
Immunosuppressed	42.8 (20.7–68.0)	25.2 (10.1–45.3)	**.002**	14 (10.4)	11 (8.6)	.62
Not immunosuppressed	40.1 (18.8–54.7)	23.0 (10.3–34.8)	**<.0001**	24 (8.0)	14 (4.8)	.11
Receiving IV vasopressors	37.6 (14.4–55.0)	20.8 (11.1–42.3)	.29	17 (23.3)	10 (17.0)	.37
Not receiving IV vasopressors	40.9 (23.1–58.5)	24.0 (10.2–36.6)	**<.0001**	21 (5.8)	15 (4.2)	.31
Concurrent infection requiring antimicrobial therapy	38.2 (15.2–50.2)	19 (6.7–37.1)	.11	6 (8.0)	4 (5.3)	.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)	.20
On-panel organism(s)	39.2 (18.0–55.5)	21.5 (10.2–35.4)	**<.0001**	28 (7.8)	22 (6.0)	.35
Off-panel organism(s)	53.8 (31.3–71.5)	48.0 (33.1–64.1)	.47	10 (13.3)	3 (5.6)	.13
Monomicrobial culture result	40.9 (22.7–58.4)	23.8 (10.3–36.7)	**<.0001**	31 (8.2)	22 (5.9)	.22
Polymicrobial culture result	43.0 (8.6–58.0)	17.9 (6.0–60.2)	.47	7 (12.1)	3 (6.4)	.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)	.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)	.14

Data points were evaluated at 96 hours after blood culture positivity and are reported as median (interquartile range), unless specified otherwise. Significant differences are highlighted in bold.

Abbreviations: AXDX, Accelerate PhenoTest BC Kit; ICU, intensive care unit; IV, intravenous.

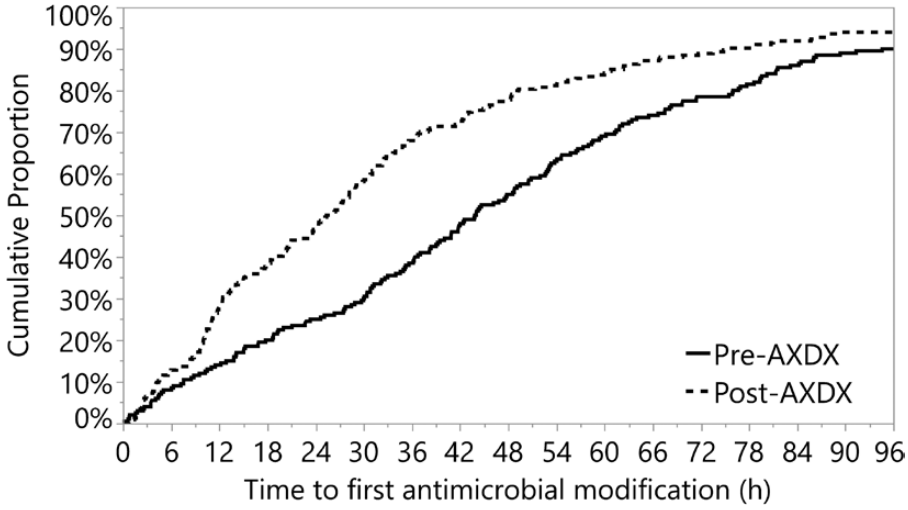

Figure 2. Kaplan-Meier analysis of the time from blood culture positivity to first antimicrobial modification. Log-rank $P < .0001$. Abbreviation: AXDX, Accelerate PhenoTest BC Kit.

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.

Table 4. Antimicrobial Modifications and Clinical Outcomes

	All[a]			Gram-Negative[b]		
Endpoint	Pre-AXDX	Post-AXDX	*P* Value	Pre-AXDX	Post-AXDX	*P* Value
Antimicrobial modification[c]						
Time to first antimicrobial modification[d]	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)	**.01**
Time to first gram-positive antimicrobial modification[e]	30.1 (11.2–52.8)	18.3 (6.7–41.8)	**.0013**	28.1 (10.5–51.7)	18.6 (9.4–42.1)	.11
Time to first gram-negative antimicrobial modification[f]	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)	**.003**
Time to first antimicrobial escalation[g]	9.5 (3.4–28.9)	9.0 (3.7–18.4)	.22	9.5 (3.7–31.6)	9.6 (3.9–18.4)	.44
Time to first antimicrobial deescalation[h]	36.0 (17.1–54.5)	27.2 (13.5–43.6)	**.0004**	34.5 (16.6–52.8)	25.4 (12.0–42.5)	**.003**
Time to effective therapy[i]	13.3 (3.1–35.9)	6.7 (3.1–16.2)	**.02**	13.7 (3.3–38.1)	10.0 (3.6–18.6)	.10
Clinical outcome						
30-day mortality	38 (8.7)	25 (6.0)	.12	25 (8.3)	19 (6.7)	.47
Post-blood culture length of stay, median (interquartile range), days	7.0 (4.0–12.4)	6.5 (3.7–12.0)	.43	6.4 (3.7–11.7)	5.4 (3.4–9.7)	**.03**
Acute kidney injury (aged ≥18 years)	92 (23.2)	78 (21.1)	.49	64 (22.7)	57 (21.6)	.76
14-day renal replacement therapy	15 (3.5)	9 (2.2)	.25	10 (3.3)	5 (1.8)	.24
30-day *Clostridioides difficile* infection (day 3–30)	3 (0.7)	4 (1.0)	.67	0	1 (0.4)	.48
Acquisition of new multidrug-resistant organisms within 30 days	22 (5.1)	15 (3.6)	.29	17 (5.7)	9 (3.2)	.15
Readmission within 30 days	76 (19.4)	91 (23.8)	.14	52 (18.6)	51 (19.4)	.82
Readmission within 30 days from bacteremia	15 (3.8)	16 (4.2)	.68	7 (2.5)	11 (4.2)	.54

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

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 nonsusceptible to at least 1 agent in ≥3 antimicrobial categories as described by Magiorakos et al [18]. (i) Extended-spectrum cephalosporin-resistant Enterobacterales defined as intermediate or resistant to a third-generation cephalosporin. (ii) Carbapenem-resistant Enterobacterales 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 nonsusceptible."

Abbreviation: AXDX, Accelerate PhenoTest BC Kit.

[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]All antimicrobial modifications data are reported as median (interquartile range), hours

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

[e]Evaluated among patients who had a gram-positive antimicrobial modification during the first 96 hours after blood culture positivity (n = 383).

[f]Evaluated among patients who had a gram-negative antimicrobial modification during the first 96 hours after blood culture positivity (n = 578).

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

[h]Evaluated among patients who had an antimicrobial deescalation during the first 96 hours after blood culture positivity (n = 581).

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

First, our study did not meet power based on prespecified mortality estimates that were used. Specifically, the 30-day mortality rate observed in the pre-AXDX arm was substantially lower (8.7%) than the rates from the published literature that was used (approximately 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%. In Randomized Trial Evaluating Clinical Impact of RAPid IDentification and Susceptibility Testing for Gram-negative Bacteremia (RAPIDS-GN), a RCT evaluating the clinical impact of AXDX in patients with GNB, an 8% mortality rate in their pre-AXDX arm was observed [4]. Babowicz et al observed a pre-AXDX 30-day mortality rate of 12.7% among patients with GNB in a single-center, quasiexperimental 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 a 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 the 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 (approximately 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 that 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 approximately 21 000 patients with BSIs and demonstrated a strong correlation between ineffective therapy and mortality (odds ratio, 1.46; 95% confidence interval, 1.43–2.40; $P < .0001$) [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 with 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 ($P = .14$), the relative difference between arms is likely of clinical significance.

While overall secondary clinical end points were not statistically different, the impact of early ID/AST results on the care of patients with BSIs was evident in subgroup analyses. There was a 1-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 that have been previously demonstrated to greatly enhance the impact of diagnostics [3, 16, 17]. At some of the study sites (Supplementary Table 1), 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 that did not implement 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 used 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 end points. Randomization as part of the study design would have likely helped to alleviate some of these imbalances between the 2 arms, making the quasiexperimental design of this study a limitation. The current study included all PBCs 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 throughout 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.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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