Analytical Performance Characteristics of the Accelerate Pheno™ System for Pathogen Identification and Susceptibility Testing for Gram-negative Bacteremia and Candidemia

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ABSTRACT

Background:
The Accelerate Pheno™ system (AXDX) is a newly FDA cleared fast diagnostic testing system that provides identification (ID) and antimicrobial susceptibility testing (AST) for microbes in positive blood culture broth. The objective of this study was to evaluate the sensitivity, specificity, and error rates of AXDX for blood cultures with yeast and Gram-negative bacilli (GNB).

Methods:
From 4/14/2016-6/1/2017, blood cultures from unique patients in the ED and medical ICU at Barnes-Jewish Hospital that signaled positive and were Gram-stain positive for GNB or *Candida* spp. were eligible. AXDX testing using pre-FDA cleared software (v1.0) was conducted in parallel with standard-of-care (SOC) diagnostic testing. SOC AST was Kirby-Bauer Disk Diffusion and/or Etest® and SOC ID was the VITEK® MS system.

Results:
Of 429 screened blood cultures, 153 met inclusion criteria; 125 had organisms that were on-panel for AXDX, 110 GNB and 15 *C. glabrata* or *C. albicans*. Non-panel organisms were other *Candida* spp. in 36.7% (11/30), other GNB in 43.3% (13/30), Gram-positive bacteria in 13.3% (4/30), and other yeast in 6.7% (2/30). For the whole cohort with MALDI-TOF as the gold standard, sensitivity for ID of GNB or yeast was 75.3%, specificity 99.7%, positive predictive value 96.0%, negative predictive value 97.6%. There were 5 false positives, including 3 *C. glabrata*, 1 each of *C. albicans* and *E. coli*. All false positive *Candida* infections were detected from specimens with *Enterobacteriaceae*. There were 10 false negatives including 3 *Pseudomonas*, 2 each of *C. glabrata* and *E. coli*, and 1 each of *Klebsiella*, *Enterobacter*, and *Proteus*. The false negative specimens with *Pseudomonas* and *C. glabrata* were monomicrobial cultures; the other false negative samples were part of polymicrobial cultures. Overall category agreement (CA) for GNB AST between AXDX and SOC was 92.0%. CA was lowest for ampicillin-sulbactam (71.8%), ceftazidime (78.7%), cefazolin (85.2%), piperacillin-tazobactam (85.6%), and tobramycin (87.6%). All other antimicrobials (amikacin, aztreonam, cefepime, ceftriaxone, ciprofloxacin, colistin, ertapenem, gentamicin, meropenem, tobramycin) had CA >93%. Post-adjudication, no very major errors were logged, major errors for 0.8% (n=8), and minor errors for 7.3% (n=86). There were 15 assay failures, including 10 failed AST, 2 failed ID, and 3 instrument technical failure. The most common reason for failure was too few clones of bacteria for analysis using AXDX (10/15, 66.7%).

Conclusions:
The Accelerate Pheno™ system is a novel fast diagnostic with high sensitivity and specificity for the ID and AST of GNB and ID of *Candida* spp. bloodstream infections that are on-panel..

INTRODUCTION

- **Fast diagnostics for identification of pathogens and antimicrobial susceptibility testing have the potential to greatly reduce time to culture reporting to physicians**
- **In order for fast diagnostics in microbiology to be widely adopted, they must achieve high sensitivity, specificity, categorical agreement for antimicrobial susceptibility testing**

METHODS

- **Design: Prospective cohort from Barnes-Jewish Hospital, a 1250 bed academic medical center in St. Louis, MO**
- **Study period: 4/14/2016-6/1/2017**
- **Inclusion criteria: ED or ICU patient with a blood culture signaling positive and Gram stain positive for GNB or yeast**
- **Exclusion criteria: age ≤18. Blood cultures meeting above criteria but signaling positive >8 hours before a research technologist was available**
- **Endpoints: sensitivity, specificity, and positive and negative predictive value for ID of GNB and yeast, category agreement and error rates for AST of GNB**

RESULTS

Figure 1: AXDX Instrument, Assay Components, and Workflow

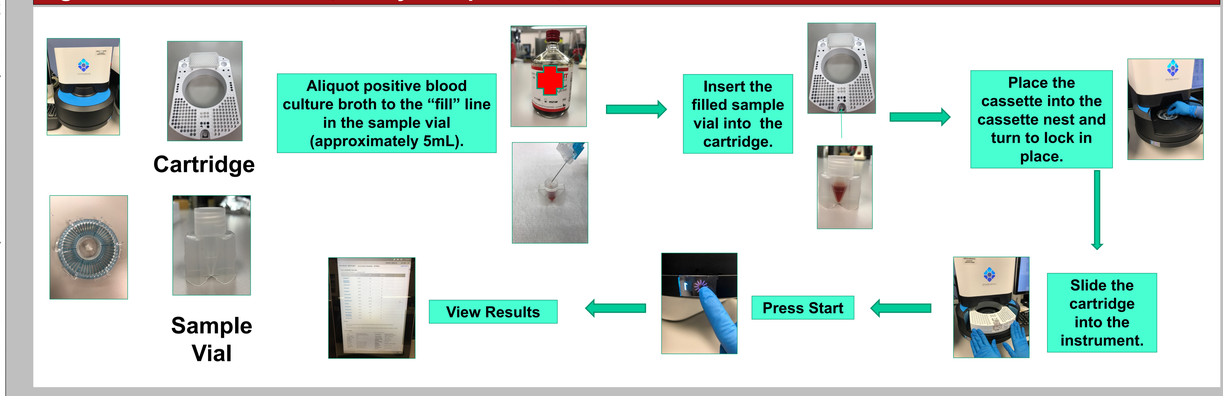
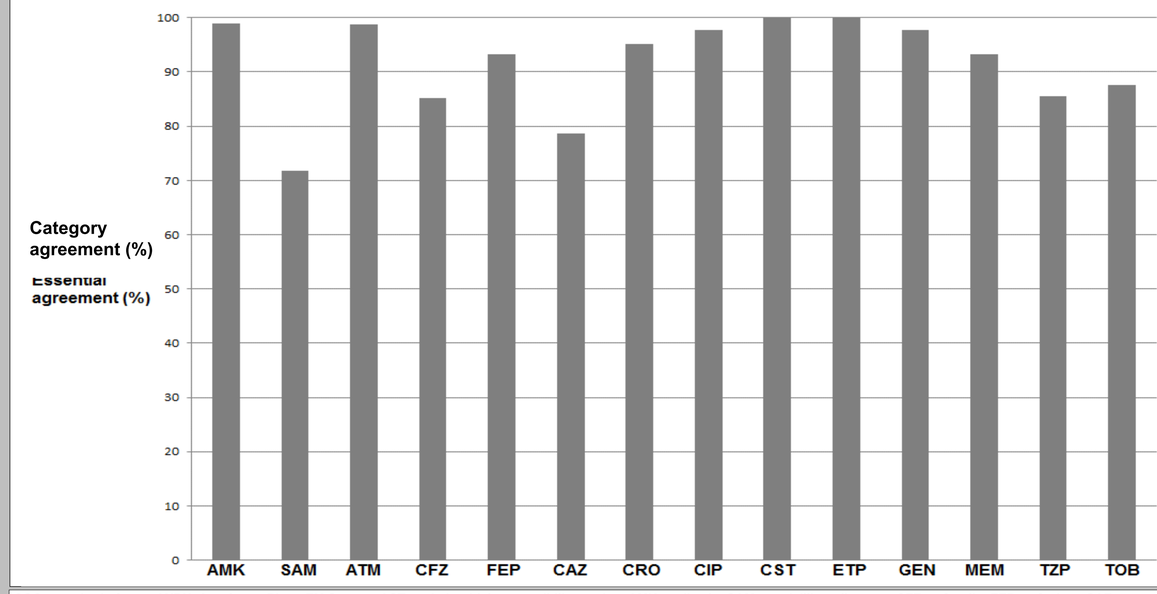


Figure 2: Category agreement between SOC and AXDX for GNB AST by tested antimicrobial



SOC: standard of care. AXDX: Accelerate PhenoTM System. AST: antimicrobial susceptibility testing. AMK: amikacin. SAM: ampicillin-sulbactam. CFZ: cefazolin. FEP: cefepime. CAZ: ceftazidime. CRO: ceftriaxone. CIP: ciprofloxacin. CST: colistin. ETP: ertapenem. GEN: gentamicin. MEM: meropenem. TZP: piperacillin-tazobactam. TOB: tobramycin.

Table 1: Sensitivity, specificity, positive and negative predictive values for AXDX as compared to SOC for GNB or yeast ID by on-panel organism

Organism	Sensitivity	Specificity	PPV	NPV
A. baumannii (n=0)	N/A	1	N/A	1
Citrobacter spp. (n=0)	N/A	1	N/A	1
Enterobacter spp. (n=10)	91.7 (59.8-99.6)	100 (99.7-100)	100 (67.9-100)	99.3 (95.6-100)
E. coli (n=42)	95.5 (83.3-99.2)	99.1 (94.3-100)	97.7 (86.2-99.9)	98.2 (92.9-99.7)
Klebsiella spp. (n=28)	96.6 (80.4-99.8)	1 (96.3-100)	100 (85.0-100)	99.2 (95.0-100)
Proteus spp. (n=11)	92.3 (62.1-99.6)	100 (96.7-100)	100 (69.8-100)	99.2 (95.5-100)
P. aeruginosa (n=12)	78.6 (48.8-94.3)	100 (96.6-100)	100 (67.9-100)	97.9 (93.5-99.5)
Serratia marcescens (n=3)	100 (30.1-100)	100 (96.9-100)	100 (31.0-100)	100 (96.9-100)
C. albicans (n=5)	100 (46.3-100)	99.3 (95.7-100)	83.3 (36.5-99.1)	100 (96.8-100)
C. glabrata (n=10)	80.0 (44.2-96.4)	97.9 (93.5-99.5)	72.7 (39.3-92.7)	98.6 (94.5-99.8)

AXDX: Accelerate PhenoTM System; GNB: Gram negative bacilli; NPV: negative predictive value; PPV: positive predictive value; SOC: standard of care.

Table 2: Sensitivity, specificity, positive and negative predictive values for AXDX as compared to SOC for GNB or yeast ID

Parameter	Whole cohort (n=153)	On-panel only (n=125)
Sensitivity	75.3 (67.8-81.8)	92.2 (85.8-96.0)
Specificity	99.7 (99.3-99.9)	99.6 (99.0-99.9)
PPV	96.0 (90.8-98.3)	95.9 (90.3-98.5)
NPV	97.6 (96.9-98.2)	99.2 (98.4-99.6)

AXDX: Accelerate Pheno™ System; CI: confidence interval; GNB: gram-negative bacilli; ID: identification; NPV: negative predictive value; PPV: positive predictive value.

Table 3: Category agreement and error rates for GNB AST.

Parameter (1158 eligible)	Number (%)
Pre-adjudication	
Category agreement (95% CI)	1055 (91.0, 89.5-92.7)
Very major errors	1 (<0.01)
Major errors	21 (1.8)
Minor errors	81 (7.0)
Post-adjudication	
Category agreement (95% CI)	1064 (92.0, 90.3-93.5)
Very major errors	0
Major errors	8 (0.8)
Minor errors	86 (7.3)

Table 4: Categorical agreement by antibiotic and organism for outliers

Organism	Antibiotic, CA	Antibiotic, CA	Antibiotic, CA
Pseudomonas (n=9)	Ceftazidime 1/9 (11.1%)	Meropenem 4/9 (44.4%)	Cefepime 7/9 (77.8%)
Enterobacter (n=6)	Cefepime 3/6 (50%)	Piperacillin-tazobactam 3/6 (50%)	
Serratia (n=3)	Ceftriaxone 0/3 (0%)	Tobramycin 2/3 (66.7%)	
Klebsiella (n=24)	Ampicillin-sulbactam 14/24 (58.3%)		
Proteus (n=11)	Tobramycin 6/11 (54.5%)		

CONCLUSIONS

- **The Accelerate Pheno™ system is a novel fast diagnostic with high sensitivity, specificity, positive and negative predictive values, and category agreement for antimicrobial susceptibility testing**
- **Prospective clinical trials are needed to evaluate the impact of this new system on clinical outcomes and antimicrobial stewardship**

ACKNOWLEDGMENTS

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