Evaluation of the Accelerate Pheno™ System: Results of a Large Academic Medical Center

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Introduction

Sepsis is a major cause of morbidity, mortality, and the most expensive condition treated in U.S. hospitals. Rapid diagnosis and susceptibility results can provide adequate therapy in a timely manner, improve outcomes and reduce costs.[1-5]

Current laboratory identification and antimicrobial susceptibility testing (AST) are based primarily on bacterial culture. Molecular testing has been used less extensively but has enabled faster pathogen identification and detection of some antimicrobial resistance genes[6], however phenotypic antimicrobial susceptibility testing (AST) is not provided.

The Accelerate Pheno™ system (Accelerate Diagnostics, Inc. Tucson, AZ) uses a broad panel of fluorescence *in-situ* hybridization assays for microorganism identification and Morphokinetic Cellular Analysis (MCA) using time-lapse imaging for antimicrobial susceptibility testing (AST). The system can identify 16 organisms (six Gram positive and eight Gram negative bacteria as well as two *Candida* species) from positive blood cultures. It provides results in 1.25 hours for identification (ID), and AST and resistance phenotypes in about 7 hours.

We present results from one academic center comparing the identification sensitivity and specificity, susceptibility testing and time to results of the Accelerate PhenoTest™ BC kit (Accelerate) to our standard of care (SOC).

Methods

From March- September 2016, 140 positive blood culture samples were included in the study and compared to our standard of care (SOC).

Blood culture bottles were incubated in the VersaTREK® system (TREK Diagnostic Systems, Cleveland, Ohio).

The SOC included subcultures of the positive blood culture bottles onto agar plates. Identification was achieved using the Microscan WalkAway-96 plus system (Microscan) (Siemens Health Diagnostics, Inc., Deerfield, Illinois) from March to 5/20/16) and MALDI-TOF (Microflex LT, Bruker Daltonics, Germany) for the subsequent months. Antimicrobial susceptibility testing was performed using Microscan panels (Pos Combo 33 and Neg/Urine 61). Accelerate testing was performed within 8 h after the blood culture bottle was flagged positive. Testing was performed according to laboratory and manufacturer procedures and used pre-FDA clearance software (v1.0).

The AST results for the SOC and Accelerate were interpreted according to the guidelines set by CLSI M100-S26.

All samples and bacterial isolates were frozen and sent to Accelerate Diagnostics for further analysis, when necessary. Additional testing for discrepant results was performed using the VITEK® 2 system (bioMérieux, France) for ID and broth microdilution for AST.

Accelerate Pheno™ system[7]

Gram Positive	ID	Ampicillin	Cefoxitin	Daptomycin	Erythromycin	Gentamicin-Streptomycin	Oxacillin	Linezolid	Vancomycin	PBP2A (Cefoxitin)	MLSb (Erythromycin-Clindamycin)
Staphylococcus aureus	X		X	X	X	X	X	X	X	X	
Staphylococcus lugdunensis	X			X	X	X	X	X	X	X	X
Coagulase-negative staphylococci[a]	X			X	X		X	X	X	X	X
Enterococcus faecalis	X	X					X	X	X		
Enterococcus faecium	X	X		X			X	X	X		
Streptococcus spp.[b]	X										
Yeast											
Candida albicans	X										
Candida glabrata	X										

[a] coagulase-negative *staphylococci* (*S. epidermidis, S. haemolyticus, S. hominis, S. capitis, S. lugdunensis, S. warneri* not differentiated)
[b] *Streptococcus* spp. (*S. mitis, S. oralis, S. gallolyticus, S. agalactiae, S. pneumoniae*, not differentiated)

X: FDA-cleared
X: RUO

Gram Negative	ID	Ampicillin - Sulbactam	Piperacillin-Tazobactam	Cefepime	Ceftazidime	Ceftriaxone	Ertapenem	Meropenem	Imipenem	Gentamicin	Tobramycin	Minocycline	Ciprofloxacin	Aztreonam	Colistin	Cefepime
Escherichia coli	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Klebsiella spp.[a]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Enterobacter spp.[b]	X		X	X	X	X	X	X	X	X			X	X	X	
Proteus spp.[c]	X	X	X	X	X	X	X	X	X	X			X	X		
Citrobacter spp.[d]	X		X	X	X	X	X	X	X	X			X	X	X	
Serratia marcescens	X		X	X	X	X	X	X	X	X			X	X		
Pseudomonas aeruginosa	X		X	X	X			X	X	X	X		X		X	
Acinetobacter baumannii	X	X	X	X				X	X			X	X		X	

[a] *Klebsiella* spp. (*K. pneumoniae, K.oxytoca*, not differentiated)
[b] *Enterobacter* spp. (*E. cloacae, E. aerogenes*, not differentiated)
[c] *Proteus* spp. (*P. mirabilis, P. vulgaris*, not differentiated)
[d] *Citrobacter* spp. (*C. freundii, C. koseri*, not differentiated)

X: FDA-cleared
X: RUO

Results: Identification and AST Performance

Figure 1: Accelerate Pheno™ system reportability

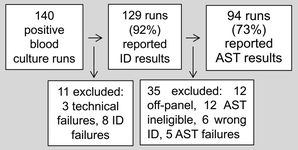

Figure 2: Runs/isolates included in analysis

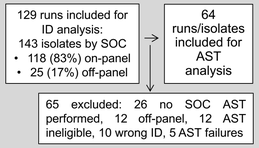

Table 1. Identification Performance

Microbe	Total Positive SOC	TP	FP	TP after discrepant analysis	TN	FN	TN after discrepant analysis	Sensitivity[a]	Specificity[b]	PPV	NPV
Gram Positive											
CNS	38	36	4	36	81	2	83	100%	95.4%	90%	100%
Enterococcus faecalis	4	4	0	4	123	0	123	100%	100%	100%	100%
Enterococcus faecium	4	3	0	3	125	1	125	75%	100%	100%	99%
Staphylococcus aureus	18	18	8	18	95	0	95	100%	92.2%	69%	100%
Staphylococcus lugdunensis	0	0	0	0	127	0	127	-	100%	-	100%
Streptococcus spp.	5	5	6	11	118	0	118	100%	100%	100%	100%
Gram Negative											
Acinetobacter baumannii	0	0	0	0	129	0	129	-	100%	-	100%
Citrobacter spp.	1	0	0	0	128	1	128	0%	100%	-	99%
Enterobacter spp.	2	2	0	2	123	0	123	100%	100%	100%	100%
Escherichia coli	14	14	0	14	115	0	115	100%	100%	100%	100%
Klebsiella spp.	12	11	0	11	116	1	116	92%	100%	100%	99%
Proteus spp.	1	1	0	1	128	0	128	100%	100%	100%	100%
Pseudomonas aeruginosa	7	5	0	5	122	2	122	71%	100%	100%	98%
Serratia marcescens	4	4	0	4	125	0	125	100%	100%	100%	100%
Yeast											
Candida albicans	1	0	0	0	128	1	128	0%	100%	-	99%
Candida glabrata	1	1	2	1	126	0	126	100%	98.4%	33%	100%
Totals											
Gram Positive	69	66	18	72	669	3	671	98.6%	98.2%	85%	99.8%
Gram Negative	41	37	0	37	986	4	986	90.2%	100%	100%	99.5%
Yeast	2	1	2	1	254	1	254	50%	99.2%	33%	99.5%
All	112	104	20	110	1909	8	1911	95%	99%	88%	99.6%

Abbreviations: CNS: Coagulase Negative *Staphylococcus* spp., TP: true positive, FP: false positive, TN: true negative, FN: false negative, PPV: Positive predictive value, NPV: Negative predictive value.
[a]Excluding 6 indeterminate results
[b]Excluding 17 indeterminate results

Table 2. AST Performance

Antibiotic	n	CA	VME	ME	MiE	Susceptible	Resistant
Gram Positive							
Ampicillin	6	6 (100%)	0 (0%)	0 (0%)	0 (0%)	4 (67%)	2 (33%)
Ceftaroline	-	-	-	0 (0%)	-	-	-
Daptomycin	27	27 (100%)	0 (0%)	0 (0%)	0 (0%)	27 (100%)	0 (0%)
Doxycycline	-	-	-	-	-	-	-
Erythromycin	22	21 (95%)	1 (6.3%)	0 (0%)	0 (0%)	6 (27%)	16 (73%)
Linezolid	28	28 (100%)	0 (0%)	0 (0%)	0 (0%)	28 (100%)	0 (0%)
Trimethoprim-Sulfamethoxazole	14	14 (100%)	0 (0%)	0 (0%)	0 (0%)	14 (100%)	0 (0%)
Vancomycin	28	28 (100%)	0 (0%)	0 (0%)	0 (0%)	27 (96%)	1 (4%)
Gram Negative							
Amikacin	36	35 (97%)	0 (0%)	0 (0%)	1 (2.8%)	34 (94%)	1 (3%)
Ampicillin-Sulbactam	24	21 (88%)	0 (0%)	0 (0%)	3 (12%)	18 (75%)	6 (25%)
Aztreonam	31	29 (94%)	1 (25%)	1 (3.7%)	0 (0%)	27 (87%)	4 (13%)
Cefazolin	23	23 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (100%)
Cefepime	36	34 (94%)	0 (0%)	0 (0%)	2 (5.6%)	4 (11%)	4 (11%)
Ceftazidime	36	28 (78%)	1 (20%)	2 (6.5%)	5 (14%)	31 (86%)	5 (14%)
Ceftriaxone	31	29 (94%)	0 (0%)	0 (0%)	2 (6.5%)	28 (90%)	3 (10%)
Ciprofloxacin	36	34 (94%)	0 (0%)	0 (0%)	2 (5.6%)	29 (81%)	7 (19%)
Colistin	-	-	-	-	-	-	-
Ertapenem	31	31 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gentamicin	36	36 (100%)	0 (0%)	0 (0%)	0 (0%)	35 (97%)	1 (3%)
Meropenem	36	30 (83%)	0 (0%)	0 (0%)	6 (17%)	35 (97%)	1 (3%)
Minocycline	-	-	-	-	-	-	-
Piperacillin-Tazobactam	36	29 (81%)	2 (33%)	0 (0%)	5 (14%)	30 (83%)	6 (17%)
Tobramycin	36	36 (100%)	0 (0%)	0 (0%)	0 (0%)	33 (92%)	3 (8%)
Totals							
Gram Positive	125	124 (99%)	1 (5.3%)	0 (0%)	0 (0%)	106 (85%)	19 (15%)
Gram Negative	428	395 (92%)	4 (6.3%)	3 (1%)	26 (6%)	304 (71%)	64 (15%)
All	553	519 (94%)	5 (6%)[a]	3 (0.7%)	26 (4.7%)	410 (74%)	83 (15%)

Abbreviations: CA: categorical agreement, VME: Very Major Errors, ME: Major Errors, MiE: Minor Errors.
Essential agreement was not included because Microscan panels and Accelerate have different reportable ranges.
[a]VME's reduced to 1 (1.2%) following discrepancy testing.

Table 3. Resistance Phenotype Testing Performance

Resistance Phenotype Markers	Count	CA	VME	ME	SOC Positive	SOC Negative
Cefoxitin & S. aureus	12	12 (100%)	-	-	8 (67%)	4 (33%)
Cefoxitin & CNS	4	3 (75%)	0 (0%)	1 (25%)	0	4 (100%)
Cefoxitin & S. lugdunensis	0	-	-	-	-	-
MLSb & CNS	0	-	-	-	-	-
MLSb & S. lugdunensis	0	-	-	-	-	-

Abbreviations: CA: categorical agreement, VME: very major errors, ME: major errors,

Discussion and Conclusions

- Accelerate PhenoTest™ BC kit provided identification and antimicrobial susceptibility testing in 92% and 73% of the eligible samples, respectively.
- Correctly identified 106 of 112 on-panel organisms and showed:
  - Sensitivity: 94.5%
  - Specificity: 99.1%
  - Positive predictive value: 88%
  - Negative predictive value: 99.6%
- The AST and resistance phenotype markers performance showed:
  - Categorical agreement: 94%
  - Very major errors: 1.2%
  - Major errors: 0.7%
  - Minor errors: 5%
  - Cefoxitin & *S. aureus* agreement: 100%
  - Cefoxitin & CNS agreement: 75%
- Identification and antimicrobial susceptibility results were an average of 36 and 44 hours faster than SOC.
- The present study shows that the Accelerate Pheno™ system is a rapid and fully automated method with high performance in identification and phenotypic antimicrobial susceptibility for microorganisms and antimicrobials represented in the assay compared to SOC methods.
- Accelerate Pheno™ system is designed based on a modular architecture and allows for one run per module. Laboratories with a large number of positive blood cultures like ours should carefully assess workflow and capacity needs before implementation.
- Additional studies are necessary to determine the real impact of a fast phenotypic antimicrobial susceptibility on clinical decision making and patient outcomes.

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