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Accelerate Pheno™ System for the Identification and Susceptibility (ID/AST) of Pathogens in Positive Blood Cultures and Impact on Time to Results and Workflow

V. Tesic, B. Hill, N. Love, S. Boonlayangoor, A. Charnot-Katsikas, K.G. Beavis

University of Chicago, Chicago, IL

THE UNIVERSITY OF CHICAGO PRITZKER SCHOOL OF MEDICINE

Kathleen G. Beavis, MD
kbeavis@bsd.uchicago.edu
773.702.3689

Introduction

The fast diagnosis of positive blood cultures is critically important to ensure the correct antibiotic therapy, maximizing the chances for an optimal outcome. Routine methods of microbial identification and susceptibility testing entail 24-48 hours, delaying the use of targeted therapy. This delay leads to increased patient morbidity, mortality, length of stay, and cost of care. Advances are needed to decrease turn-around-time of blood culture results. Methods such as MALDI-TOF, PNA-FISH, and multiplex PCR are rapid but have limited ability, at best, to produce a susceptibility result. The Accelerate Pheno™ system uses a fully automated fluorescence *in situ* hybridization technology to provide fast species identification and morphokinetic cellular analysis (MCA) to provide fast antimicrobial susceptibility results for the most commonly identified organisms in bloodstream infections.

Materials and Methods

296 positive blood culture specimens collected from patients at the University of Chicago Medicine were tested within 8 hours of positivity on the Accelerate Pheno™ system from March 2016 to October 2016. Only one positive blood culture per patient was included in the study.

We evaluated the accuracy and turnaround time of bacterial and yeast ID/AST using the Accelerate Pheno™ system (v1.0 pre-FDA clearance software) in the clinical microbiology laboratory compared to current methods (VITEK® MS, VITEK® 2, Kirby-Bauer and/or E-test) by measuring sensitivity and specificity for ID and essential (EA) and/or categorical agreement (CA) for AST. Very Major Errors (VME) were defined as isolates testing Susceptible by the Accelerate method and Resistant by current testing methods. Major Errors (ME) were defined as isolates testing Resistant by the Accelerate method and Susceptible by current testing methods. The average time to ID/AST results and workflow analysis was calculated for the Accelerate Pheno™ system and compared to the standard of care.

Results

Of the 296 blood cultures, 64 were excluded from further analysis due to technical failures, time lapse of more than 8 hours after positivity of blood culture or no final identification performed by routine method in the laboratory. Out of the remaining 232 blood cultures (221 monomicrobial, 11 polymicrobial), sensitivity and specificity for identification of Gram-positive bacteria was 95.6% and 99.1%, Gram-negative bacteria 95.3% and 99.9% and yeast 100% and 98.9%, respectively. Overall sensitivity and specificity was 95.6% and 99.5% (Table 1). The false positive rate for Gram-positives was 0.7% (n=10), for Gram-negatives 0.1% (n=1), for yeast 1.1% (n=5) and overall the false positive rate was 0.4% (n=16). The false negative rate for Gram-positives was 0.4% (n=5), for Gram-negatives 0.2% (n=4), for yeast 0% (n=0) and overall the false negative rate was 0.2% (n=9).

Of 154 isolates evaluated for AST, essential agreement was obtained in 94.8% and categorical agreement in 95%. For the 77 Gram-positive organisms, 232 total drug/bug combinations were evaluated for both EA (97%, range 93%-100%) and CA (98.7%, range 93%-100%). There were no VMEs or MEs and 3 minor errors (MiE) (Table 2a). Cefoxitin performed well for the detection of methicillin resistance in the coagulase-negative staphylococci (CA= 97.5%) and in *S. aureus* (CA= 100%) (Table 3). For the 77 Gram-negative organisms, 695 and 708 total drug/bug combinations were analyzed for overall EA (94.1%) and CA (93.8%), respectively. There were 0 VME, 8 ME, and 36 MiE. Of the MiEs, 25 (69%) were reported as being more resistant by the Accelerate method (Table 2b).

The majority of drug-bug results analyzed (n=642) were for the Enterobacteriaceae, for which EA was 94.1% (range 70.3% - 100%) and CA was 93.8% (range 70.3%-100%). *Pseudomonas aeruginosa* and *Acinetobacter baumannii* comprised the remaining isolates evaluated. For *P. aeruginosa* (n=55), EA and CA ranged from 62.5%-100%; for the few *A. baumannii results* available (n=11), CA was 100% for all drugs tested (EA was not applicable, as testing per our current methods was performed by disk diffusion).

Time to identification and susceptibility was reduced by 23.5 and 41.9 hours, respectively; hands-on time was reduced by 32 min.

Conclusions

The Accelerate Pheno™ system provides fast and accurate results for most of the organisms found routinely in blood cultures. Failure to identify species was due in most cases to low organism number or the presence of an atypical organism not found on the Accelerate panel. The Accelerate Pheno™ system is easy to use, reduces hands-on time for ID/AST of common blood pathogens, and allows clinically actionable results to be released much earlier than the current standard of care. For antimicrobial susceptibility, the Accelerate Pheno™ system performed comparably to our current AST test methodologies for the majority of drug-bug combinations. However, additional testing is needed for some organisms (i.e. *Acinetobacter baumannii* and carbapenemase-producing Gram-negatives) and drug-bug combinations (i.e. colistin against the Gram-negative isolates) that were underrepresented.

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ID and AST Performance

Table 1: *Identification Performance (n=232 runs)*

Organism	Sensitivity[a]		Specificity[b]	
Gram-Positive				
Coagulase-negative *Staphylococcus* spp.	52/52	100%	169/172	98.3%
Enterococcus faecalis	15/17	88.2%	215/215	100%
Enterococcus faecium	3/5	60%	227/227	100%
Staphylococcus aureus	18/19	94.7%	200/202	99%
Staphylococcus lugdunensis	0/0	N/A	228/228	100%
Streptococcus spp.	21/21	100%	205/210	97.6%
TOTAL	**109/114**	**95.6%**	**1244/1254**	**99.1%**
Gram-Negative				
Acinetobacter baumannii	3/3	100%	229/229	100%
Citrobacter spp.	2/2	100%	230/230	100%
Enterobacter spp.	11/13	84.6%	215/216	99.5%
Escherichia coli	30/31	96.8%	201/201	100%
Klebsiella spp.	20/21	95.2%	211/211	100%
Proteus spp.	3/3	100%	229/229	100%
Pseudomonas aeruginosa	9/9	100%	223/223	100%
Serratia marcescens	3/3	100%	229/229	100%
TOTAL	**81/85**	**95.3%**	**1767/1768**	**99.9%**
Yeast				
Candida albicans	2/2	100%	229/229	100%
Candida glabrata	3/3	100%	224/229	97.8%
TOTAL	**5/5**	**100%**	**453/458**	**98.9%**
Overall	**195/204**	**95.6%**	**3464/3480**	**99.5%**

[a]7 indeterminate results excluded from sensitivity calculation
[b]20 indeterminate results excluded from specificity calculation

Table 2a: *AST Performance for Gram-Positive Organisms**

Antibiotic	EA		CA		VME	ME	MiE	S	I	R
Staphylococcus aureus										
Erythromycin	15/16	93.8%	15/16	93.8%	0	0	1	9	1	6
Linezolid	16/16	100%	16/16	100%	0	0	0	16	0	0
Trimethoprim-Sulfamethoxazole[†]	16/16	100%	16/16	100%	0	0	0	16	0	0
Vancomycin	15/16	93.8%	16/16	100%	0	0	0	16	0	0
TOTAL	**62/64**	**96.9%**	**63/64**	**98.4%**	**0**	**0**	**1**	**57**	**1**	**6**
Coagulase-Negative *Staphylococcus* spp.										
Erythromycin[†]	44/45	97.8%	44/45	97.8%	0	0	1	17	0	28
Linezolid[†]	46/47	97.9%	47/47	100%	0	0	0	47	0	0
Vancomycin	44/46	95.7%	46/46	100%	0	0	0	46	0	0
TOTAL	**134/138**	**97.1%**	**137/138**	**99.3%**	**0**	**0**	**1**	**110**	**0**	**28**
***Enterococcus* spp.**										
Ampicillin	8/8	100%	8/8	100%	0	0	0	7	0	1
Linezolid	8/8	100%	8/8	100%	0	0	0	7	0	1
Vancomycin	13/14	93%	13/14	93%	0	0	1	12	0	2
TOTAL	**29/30**	**96.7%**	**29/30**	**96.7%**	**0**	**0**	**1**	**26**	**0**	**4**
Overall	**225/232**	**97%**	**229/232**	**98.7%**	**0**	**0**	**3**	**192**	**1**	**39**

Table 2b: *AST Performance for Gram-Negative Organisms**

Antibiotic	EA		CA		VME	ME	MiE	S	I	R
Enterobacteriaceae										
Amikacin	61/61	100%	61/61	100%	0	0	0	60	0	1
Ampicillin-Sulbactam	26/37	70.3%	26/37	70.3%	0	6[‡]	5	22	5	10
Cefazolin[†]	42/47	89.4%	40/47	85.1%	0	0	7	0	40	7
Cefepime	59/63	93.7%	59/63	93.7%	0	0	4	58	2	3
Ceftazidime	52/62	83.9%	55/62	88.7%	0	1	6	53	0	9
Ceftriaxone	62/62	100%	60/62	96.8%	0	0	2	54	0	8
Ciprofloxacin	61/62	98.4%	60/62	95.2%	0	0	2	45	1	16
Colistin[†]	N/A[††]		N/A[††]		1/1	100%	0	0	1	0	0
Ertapenem	62/63	98.4%	59/63	93.7%	0	1	3	60	2	1
Gentamicin	60/63	95.2%	63/63	100%	0	0	0	56	1	6
Meropenem	60/60	100%	60/60	100%	0	0	0	59	0	1
Tobramycin	58/61	95.1%	58/61	95.1%	0	0	3	50	6	5
TOTAL	**603/641**	**94.1%**	**602/642**	**93.8%**	**0**	**8**	**32**	**518**	**57**	**67**
Pseudomonas aeruginosa										
Amikacin	8/8	100%	8/8	100%	0	0	0	7	0	1
Cefepime	8/8	100%	7/8	100%	0	0	1	7	0	1
Ceftazidime	7/8	87.5%	5/8	62.5%	0	0	3	4	2	2
Ciprofloxacin	7/7	100%	7/7	100%	0	0	0	6	0	1
Colistin[†]	N/A[††]		N/A[††]		1/1	100%	0	0	1	0	0
Gentamicin	6/8	75%	8/8	100%	0	0	0	7	0	1
Meropenem	8/8	100%	8/8	100%	0	0	0	7	0	1
Tobramycin	7/7	100%	7/7	100%	0	0	0	6	0	1
TOTAL	**51/54**	**94.4%**	**51/55**	**92.7%**	**0**	**0**	**4**	**45**	**2**	**8**
Acinetobacter baumannii										
Amikacin	N/A	N/A	2/2	100%	0	0	0	2	0	0
Ampicillin-Sulbactam[†]	N/A	N/A	2/2	100%	0	0	0	2	0	0
Cefepime[†]	N/A	N/A	2/2	100%	0	0	0	2	0	0
Ciprofloxacin[†]	N/A	N/A	2/2	100%	0	0	0	2	0	0
Meropenem[†]	N/A	N/A	2/2	100%	0	0	0	2	0	0
Piperacillin-Tazobactam	N/A	N/A	1/1	100%	0	0	0	1	0	0
TOTAL	**N/A**	**N/A**	**11/11**	**100%**	**0**	**0**	**0**	**11**	**0**	**0**
Overall	**654/695**	**94.1%**	**664/708**	**93.8%**	**0**	**8**	**36**	**574**	**59**	**75**

Table 3: *Resistance Phenotype Performance**

Combination	Count	CA		VME	ME	S	R
Cefoxitin & *S. aureus*	17	17/17	(100%)	0	0	10	7
Cefoxitin & CNS	40	39/40	(97.5%)	1	0	16	24

*Results based on CLSI 2016 breakpoints
[†] RUO
[††] Colistin tested by disk diffusion
[‡]For each ME, Accelerate had an MIC of 32, VITEK 2 had an MIC of 16. 3 ME's had a broth microdilution result of 8, such that all results were around the breakpoints. 3 ME's had a broth microdilution result of <=1 which matches neither Accelerate nor VITEK 2.

Workflow Comparison: Current vs. Accelerate Pheno™ System

	Hands-On Time					Time To	
	Gram Stain and MD Notification	Sub-Culture	ID Setup	AST Setup	TOTAL	ID	AST
Current (VITEK MS, VITEK 2, KB, E-Test)	19 min	5 min and 24 h* incubation	8 min and 22 min* instrument time	3.5 min and 24 h* incubation	35.5 min	24.9 h	49 h
Accelerate Pheno™ System	N/A	N/A	3.5 min and 1.4 h* instrument time	N/A and 5.7 h* incubation	3.5 min	1.4 h	7.1 h
Time Difference	**19 min**	**5 min**	**4.5 min**	**3.5 min**	**32 min**	**23.5 h**	**41.9 h**

*No Hands-On Time