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SUSCEPTIBILITY PROVISION ENHANCES EFFECTIVE DE-ESCALATION (SPEED). UTILIZING RAPID PHENOTYPIC SUSCEPTIBLITY TESTING IN GRAM-NEGATIVE BLOODSTREAM INFECTIONS AND ITS POTENTIAL CLINICAL IMPACT

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INTRODUCTION

Currently, pathogen identification (ID) and antimicrobial susceptibility testing (AST) rely primarily on culture-based methods, often taking >48 hours for results.

- There is a critical need for rapid and reliable diagnostics for the timely selection of antimicrobial therapy and enhanced antimicrobial stewardship.
- The Accelerate Pheno™ system (AXDX) is a new technology that quickly identifies the most common organisms in bloodstream infections by utilizing morphokinetic cellular analysis to provide rapid AST results.
- The aim of this study was to compare pathogen ID, AST, and turnaround times (TATs) of AXDX against current standard of care (SOC) methods.
- Secondarily, we assessed the potential time to active and optimal antibiotic therapy if the AXDX was utilized with gram-negative rod (GNR) bacteremia.

METHODS

Enrollment
Positive blood culture samples from all patients admitted to Riley Hospital for Children and associated Indiana University Health Hospitals with monomicrobial GNR bacteremia were prospectively enrolled over a 3-month timespan.

Pathogen ID, AST and TAT
Standard of care laboratory methods for pathogen ID (VERIGENE® and Bruker MALDI Biotyper® systems) and AST (VITEK® 2 system) were run in tandem with the Accelerate PhenoTest™ BC kit (Fig 1) on positive blood culture samples (BACTEC® FX). Testing used the Accelerate Pheno™ system software version 1.3.1.15.

- Exclusion criteria included samples with off-panel organisms or recurrent bacteremia within 30 days.
- ID positive percent agreement (PPA) and negative percent agreement (NPA) were calculated for on-panel target organisms.
- AST essential agreement (EA), categorical agreement (CA), major errors (ME), and very major errors (VME) were calculated.
- Turnaround times of patient results were compared between AXDX and conventional methods.

Theoretical Clinical Data
Demographic and clinical data, including selection and timing of antibiotics, were collected on all eligible patients.

- Exclusion criteria included samples with an off-panel organism, contaminated/impure growth, or a concurrent infection site that grew at least 1 organism that was not isolated from blood.
- Active therapy was defined as the first antimicrobial dose to which blood culture organism was susceptible by conventional antimicrobial testing.
- Optimal therapy was defined as the earliest optimal dose of antimicrobial therapy from time of blood culture positivity.
- Cases that did not fall within evidence-based guidelines were adjudicated by an infectious diseases physician.
- Time to active and optimal therapy were compared to time when AXDX ID and AST results were available.

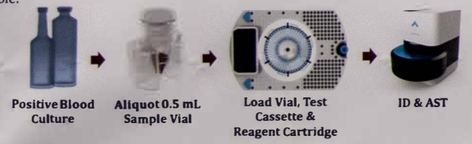

Figure 1: The Accelerate Pheno™ system workflow
A 0.5 mL blood aliquot was placed in the sample vial and run on AXDX. Eligible bacteria were exposed to a panel of antimicrobials, and the system analyzed bacterial growth to determine susceptibility based on morphokinetic cellular analysis.

RESULTS

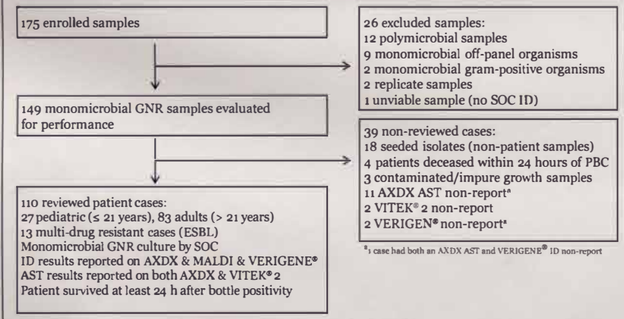

Figure 2. Flow diagram of study design and population inclusivity criteria

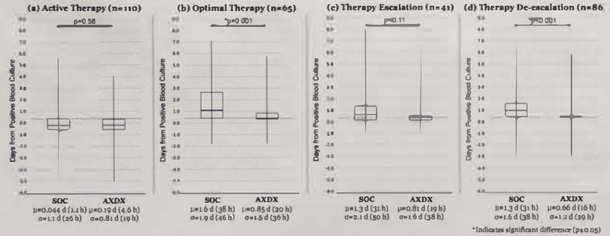

Figure 3. All-patient therapy intervention times, SOC compared to theoretical AXDX for (a) active therapy, (b) optimal therapy when possible, (c) first escalation of therapy when required, and (d) first de-escalation of therapy when possible. Box plots display median and interquartile ranges (IQR) with tails indicating the minimum and maximum of observed values, and notes mean (μ) and standard deviation (σ). Grey dashed line represents mean AXDX AST time (9.0 h) for reference.

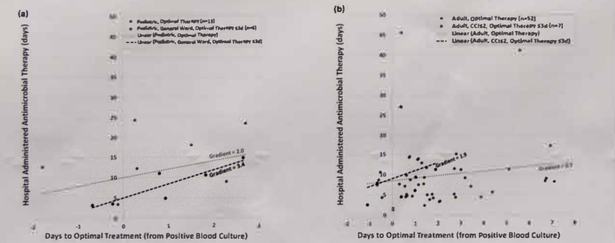

Figure 4. Patients who received optimal therapy relative to positive blood culture in (a) pediatric patients highlighting cases optimized within three days in general wards and (b) adult patients highlighting cases optimized within three days with CCI ≤2.

Table 1. Characteristics for case-reviewed patient populations.

Category	Description	Total Cases (n=110)	Pediatric Cases (n=27)	Adult Cases (n=83)
Pathogen	*E. coli*	56 (51%)	8 (30%)	48 (58%)
	Klebsiella spp.	26 (24%)	10 (37%)	16 (19%)
	*Enterobacter*spp.	11 (10%)	6 (22%)	5 (6%)
	P. aeruginosa	9 (8%)	3 (11%)	6 (7%)
	A. baumannii	3 (3%)	-	3 (4%)
	*Citrobacter*spp.	3 (3%)	-	3 (4%)
	Proteus spp.	2 (2%)	-	2 (2%)
Gender	Female	50 (45%)	13 (48%)	37 (45%)
	Male	60 (55%)	14 (52%)	46 (55%)
Age	1 month <1 year	5 (5%)	5 (19%)	-
	≥1 year ≤18 years	19 (17%)	19 (70%)	-
	>18 year ≤21 years	3 (3%)	3 (11%)	-
	>21 year <50 years	14 (13%)	-	14 (17%)
	≥50 year <60 years	21 (19%)	-	21 (25%)
	≥60 year <70 years	20 (18%)	-	20 (24%)
	≥70 year <80 years	18 (16%)	-	18 (22%)
	≥80 year	10 (9%)	-	10 (12%)
Admission Service	Hematology/Oncology	13 (12%)	8 (30%)	5 (6%)
	Critical Care	10 (9%)	2 (7%)	8 (10%)
	Transplant	14 (13%)	5 (19%)	9 (11%)
	General Wards	73 (66%)	12 (44%)	61 (73%)
Intensive Care	ICU Visit During Therapy	36 (33%)	7 (26%)	29 (35%)
	No ICU Visit	74 (67%)	20 (74%)	54 (65%)

Table 2. ID performance of AXDX vs. MALDI-TOF MS and VERIGENE® system.

Microbe	PPA[a]	NPA[b]
E. coli	64/64 (100%)	83/83 (100%)
Klebsiella spp.	32/32 (100%)	115/116 (99.1%)
*Enterobacter*spp.	16/19 (84.2%)	130/130 (100%)
Proteus spp.	4/5 (100%)	144/144 (100%)
*Citrobacter*spp.	4/5 (80%)	144/144 (100%)
S. marcescens	2/2 (100%)	147/147 (100%)
A. baumannii	4/4 (100%)	145/145 (100%)
P. aeruginosa	16/17 (94.1%)	131/131 (100%)
Total	142/148 (95.9%)	1039/1040 (99.9%)

[a]1 indeterminate result (*E. coli*) was excluded from PPA calculation
[b]3 indeterminate results (1 for *E. coli*, 1 for *Klebsiella* spp., and 1 for *P. aeruginosa*) were excluded from NPA calculation

Table 3. Mean time to assay result by method (n=110).

Assay	Method	Instrument Run Time[a]	Time from Positivity [a]
ID	VERIGENE®	2.0 ± 0.4	4.4 ± 1.7
	MALDI-TOF MS	N/A	21 ± 7.2
	AXDX	1.3 ± 0.01	3.7 ± 1.7
AST	VITEK® 2	9.2 ± 1.4	35 ± 7.7
	AXDX	6.6 ± 0.05	9.0 ± 1.7

[a]Times presented are mean ± standard deviation (σ) in hours. n=110 for all results, p<0.001 between all assay-method time to results.

SUMMARY OF RESULTS

ID Performance
- The Accelerate Pheno™ system had a PPA of 95.9% and a NPA of 99.9% for pathogen identification compared to both the VERIGENE® system and the Bruker MALDI Biotyper® system (Table 2).

AST Performance
- AXDX had an EA and CA of 94.5% and 93.5%, respectively, for adjudicated AST compared to the VITEK® 2 system (data not shown).
- All CA errors were minor, with the exception of 6 major errors (1 for ampicillin-sulbactam, 1 for cefepime, 2 for ceftazidime and 2 for meropenem) and 1 very major error for piperacillin-tazobactam.

Time to Result
- Mean time from set-up to ID was 1.3 h for AXDX compared to 2.0 h for the Verigene® system. Mean time from set-up to AST result was 6.6 h for AXDX compared to 9.2 h for VITEK® 2 system (Table 3).
- Mean time from positivity to ID was 3.7 h for AXDX compared to 4.4 h for Verigene® and 21.0 h for MALDI-TOF MS confirmatory testing. Mean time from positivity to AST result was 9.0 h for AXDX compared to 35.0 h for the VITEK® 2 system
- AXDX instrument timing is more consistent than VITEK® 2 based on standard deviations (Table 3).

Theoretical Clinical Outcomes
- AXDX-derived AST results (minimum of 9.0 h after positivity) for all cases showed a theoretical mean time to de-escalation from time of positive cultures to be 0.66 days (16 h) compared to 1.3 days (31 h) for current SOC (p<0.001) (Figure 3d).
- 25% (28/110) of patients could have theoretically been put on active therapy sooner (minimum of 9.0 h after positivity) if the AXDX AST results had been clinically available (Figure 3a).
- 59% of reviewed cases (65/110) had therapy optimized during hospitalization (Figure 3b).
  - Of these, 78% (51/65) of patients could have had therapy optimized earlier had AXDX AST results been available (Figure 3b).
- Each day to optimize patient therapy could correlate to a 3.4 or 1.9-day reduction in overall treatment time across pediatric general ward patients or adult patients with CCI ≤2, respectively, when therapy optimized within 3 days (Figure 4).

CONCLUSIONS

- Diagnostic modalities with rapid ID and AST results have the potential to decrease time to de-escalation, along with time to active and optimal therapy, thus impacting clinical care and aiding in effective antimicrobial stewardship.
- The Accelerate Pheno™ system provides fast and reliable results compared to conventional laboratory methods.
- Prospective studies evaluating the clinical impact of AXDX on patient outcomes are needed and planned.

ACKNOWLEDGEMENTS

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TRANSPARENCY DECLARATIONS

*N.W.S. has stock options an is an employee of Accelerate Diagnostics, Inc. N.W.S. was involved in data management, figure design, and manuscript preparation. All other authors: none to declare.