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Evaluation of the Accelerate Pheno™ System for clinical decision-making in Gram-negative bacillary bloodstream infections

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ABSTRACT

Introduction: The Accelerate Pheno™ system (AXDX) is a rapid diagnostic tool capable of performing identification (ID) and antimicrobial susceptibility testing (AST) on positive blood cultures within 7 hours. Previous studies regarding AXDX have shown significant reductions in time to ID and AST. However, the AXDX AST currently lacks FDA-approval for narrow-spectrum agents such as cefazolin and ampicillin. Therefore, the purpose of this study will be to assess the potential clinical impact of the utilization of AXDX on antimicrobial selection.

Methods: This is a retrospective comparison of AXDX and standard of care (SOC) procedures applied to monomicrobial blood cultures with Gram-negative bacilli on Gram stain. Blood cultures from the institutional validation of the AXDX system between January and April 2017 were utilized in this study. Organisms unidentified by AXDX were excluded. SOC included biochemical assays, Vitek 2, and MALDI-TOF. Outcomes assessed included: time to ID/AST, rate of categorical (CA) and essential agreement (EA), rates of very major, major and minor error, and the narrowest susceptible beta-lactam of each method.

Results: Of the 30 samples screened, 22 met inclusion criteria. *Escherichia coli* and *Klebsiella spp.* accounted for 41% (9/22) and 18% (4/22), respectively; *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Serratia marcescens* were each isolated twice; *Citrobacter freundii*, *Citrobacter koseri*, and *Enterobacter cloacae* were each isolated once. AXDX reduced the time to ID and AST by 24.1 (p<0.001) and 29.3 hours (p<0.001), respectively. AST results demonstrated 92% CA and 91% EA between each method. Among beta-lactams, AXDX reported ceftriaxone and ampicillin/sulbactam as the narrowest agent for 46% (6/13) and 39% (5/13), respectively, for all *E. coli* and *Klebsiella* isolates. Narrower therapeutic options were available by SOC as compared to AXDX for 89% of E. coli isolates (8 cefazolin-susceptible, 5 ampicillin-susceptible). All *Klebsiella spp.* were cefazolin-susceptible.

Conclusion: AXDX provided faster time to organism ID and AST but limited the opportunity to de-escalate to the narrowest spectrum beta-lactam in more than half of cases, particularly in the setting of *E. coli* bacteremia. While AXDX complements antimicrobial stewardship activities by promoting earlier active antimicrobial administration; SOC methods remain necessary to optimize definitive antimicrobial therapy.

INTRODUCTION

- Gram-negative bacilli (GNB) are a major cause of bloodstream infections (BSI) with mortality rates of 35-50% in the intensive care setting.[1] Inadequate empiric antimicrobial therapy has also been associated with increased mortality.[2]
- A recent audit of our institution's management of GNB BSI revealed that empiric antimicrobial therapy was active in 89% of cases but empiric anti-pseudomonal therapy was unnecessary in 88% of cases. Thirty-six and 90% of antimicrobial susceptibility testing (AST) results were available at 48 and 72 hours, respectively.
- Accelerate Pheno™ System (AXDX) is a rapid diagnostic tool capable of providing organism identification (ID) and AST within 2 and 7 hours, respectively. AXDX lacks ampicillin AST as well as FDA-approval for cefazolin AST for GNB.
- AXDX detects the following GNB: *Acinetobacter baumannii, Citrobacter spp., Enterobacter spp., Escherichia coli, Klebsiella spp., Proteus spp., Pseudomonas aeruginosa,* and *Serratia marcescens.*
- The purpose of this study was to assess the performance characteristics and potential clinical impact of AXDX on antimicrobial selection.

METHODS

Inclusion criteria: GNB isolates from blood cultures used in validation of the AXDX platform by Clinical Microbiology from Jan 2017 to Apr 2017 at the UVA Health System were included. SOC methods included biochemical analysis, Vitek 2, and MALDI-TOF.

Exclusion criteria: Polymicrobial, AXDX organism identification failure, AXDX and SOC initiation times >24 hours apart

Primary Objective: Concordance of narrowest possible beta-lactam for each method (in order, beginning with the most narrow spectrum): ampicillin (SOC only), cefazolin (SOC only), ampicillin/sulbactam, ceftriaxone, piperacillin/tazobactam or cefepime, carbapenem

Secondary Objectives: 1) Time to ID/AST for SOC and AXDX, 2) rates of categorical and essential agreement, very major, major and minor errors

RESULTS

Figure 1. Study enrollment and design

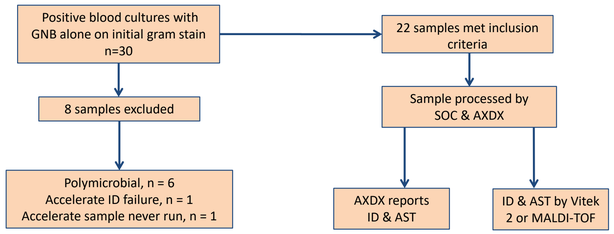


Figure 2. Narrowest beta-lactam reported susceptible for *E. coli* and *Klebsiella spp.* isolates

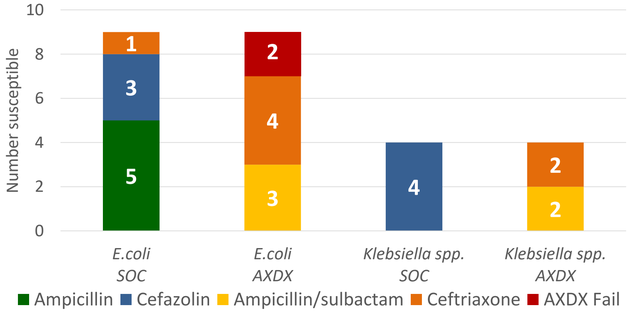


Table 1. Overall CA and EA between SOC and AXDX

Antimicrobial	Essential agreement	Categorical agreement
Amikacin, n=18	18 (100)	18 (100)
Ampicillin-sulbactam, n=11	8 (73)	8 (73)
Aztreonam, n=16	12 (75)	14 (88)
Cefepime, n=18	16 (89)	18 (100)
Ceftazidime*, n=10	---	6 (60)
Ceftriaxone, n=16	16 (100)	14 (88)
Ciprofloxacin, n=18	17 (94)	18 (100)
Ertapenem, n=16	16 (100)	16 (100)
Gentamicin, n=18	18 (100)	17 (94)
Meropenem, n=18	15 (83)	16 (89)
Piperacillin-tazobactam, n=16	13 (81)	13 (81)
Tobramycin, n=18	17 (94)	17 (94)
Total, n=193	**166 (86)**	**175 (91)**

*Data presented as n (%); **Ceftazidime was evaluated using E-test only

Figure 3. Time to ID & AST from positive blood culture

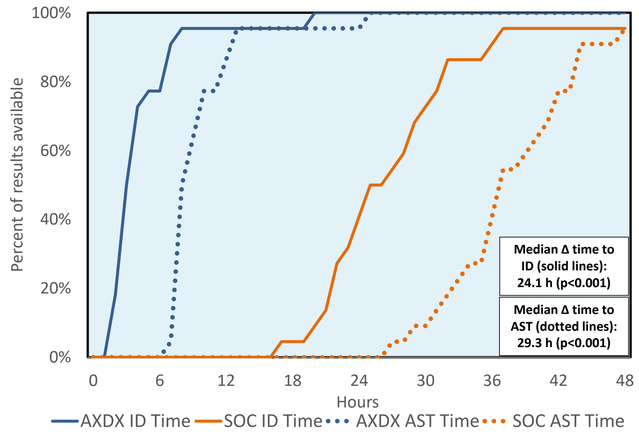
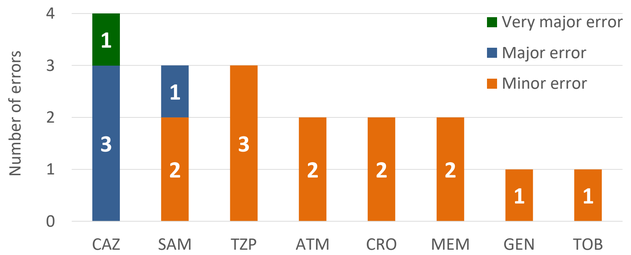


Figure 4. Number of errors per antimicrobial



SAM: ampicillin-sulbactam; ATM: aztreonam; CAZ: ceftazidime; CRO: ceftriaxone; GEN: gentamicin; MEM: meropenem; TZP: piperacillin-tazobactam; TOB: tobramycin

- Organisms identified include: *E. coli* (n=9), *E. aerogenes* (n=2), *K. pneumoniae* (n=2), *K. oxytoca* (n=2), *P. aeruginosa* (n=2), *S. marcescens* (n=2), *C. freundii* (n=1*), C. koseri* (n=1), *E. cloacae* (n=1). AXDX failed to identify the *C. freundii* and *E. cloacae* isolates.
- Apart from *E.coli* and *Klebsiella spp.,* narrowest-spectrum beta-lactam therapy was concordant for all organisms except one *S. marcescens* isolate for which SOC reported ceftriaxone as the most narrow agent while AXDX reported ceftriaxone as 'intermediate'.
- Ciprofloxacin had concordant AST results between AXDX and SOC when excluding the 4 AXDX AST failures (100%, 18/18). Fifteen isolates were ciprofloxacin-susceptible while 3 were reported as 'intermediate' or 'resistant' by both methods.

DISCUSSION

- Narrower therapeutic options were available by SOC for 89% of *E. coli* isolates (8/9) and all *Klebsiella spp.* isolates (4/4) compared to AXDX. This was driven by ampicillin and cefazolin AST via SOC methods which were susceptible among 33% (3/9) and 56% (5/9) of *E.coli* isolates, respectively. All *Klebsiella spp.* were susceptible to cefazolin (100%, 4/4).
- For AXDX, ceftriaxone and ampicillin/sulbactam were reported as the narrowest beta-lactam for 46% (6/13) and 39% (5/13), respectively, for all *E. coli* and *Klebsiella* isolates.
- AXDX reduced the mean time from positive blood culture to ID and AST results by 24.1 and 29.3 hours, respectively (p<0.001 for both comparisons).
- For all organism-antimicrobial combinations the error rate was 9.3% (18/193). Ceftazidime accounted for the most MEs (75%, 3/4) as well as the only VME.
- Limitations: 1) Low number of isolates; minimal diversity, 2) The term 'narrow-spectrum' used in this study is a subjective definition, 3) Real-time antimicrobial decision-making was not assessed, 4) Patient-specific characteristics were not incorporated into antimicrobial selection.

CONCLUSIONS

- AXDX provided faster time to organism identification but limited the opportunity to de-escalate to the narrowest spectrum beta-lactam in more than half of cases in this small data set.
- AXDX complements antimicrobial stewardship activities by promoting the earlier administration of active antimicrobials.
- SOC AST methods remain necessary to optimize definitive therapy for most *E. coli* and *Klebsiella spp.* due to the lack of ampicillin and cefazolin AST on AXDX.
- Major and very major errors were driven by ceftazidime and otherwise uncommon.
- Future studies are needed to assess the real-time impact of AXDX implementation on antimicrobial selection and patient outcomes.

REFERENCES

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2. Retamar P, Portillo MM, Lopez-Prieto MD, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother. 2012; 56(1):472-8.

Disclosures: Dr. Amy Mathers serves as a consultant for Accelerate Diagnostics, Inc. All other authors have nothing to disclose with commercial entities that may have a interest in the subject matter of this presentation.