Rapid antimicrobial susceptibility testing of Gram-negative species directly from positive blood cultures using a novel holographic imaging system

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INTRODUCTION

- Sepsis is the most significant source of mortality and cost in hospitals worldwide.[1,2]
- Early detection and treatment of pathogens causing bloodstream infections that can lead to sepsis is important to optimize treatment and improve the chance of survival.
- Antimicrobial resistance exacerbates the clinical challenge of treating up to 1 in 3 patients with bloodstream infections depending on the causative organism.[3]
- Traditional identification (ID) and antimicrobial susceptibility testing (AST) methods can take days to provide results.

The Accelerate WAVE™ system*

- The Accelerate WAVE™ system* (Figure 1) is a new AST platform under development that utilizes holographic imaging of individual cell responses to antimicrobials over time. It can measure and quantify growth, morphological and other responses to antimicrobials to provide an MIC result based upon the species ID (obtained from a separate method).
- The Accelerate WAVE™ system* has the potential to offer the following advantages:
  - AST results directly from positive blood cultures (PBC) and isolates
  - MIC result reporting for Gram-negative organisms within 4.5 hours
  - Faster, same-shift reporting of AST results vs. traditional methods

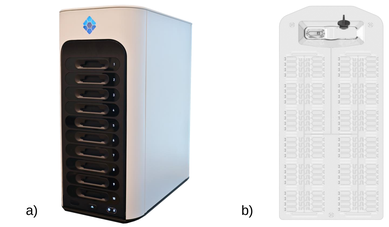

*Figure 1. Accelerate WAVE™ a) module and b) GN PBC card**

- In this development study, we present how the MIC algorithms were built for the Accelerate WAVE™ system* and preliminary performance results for Gram-negative organisms.

REFERENCES

1. Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *The Lancet* 2020; doi: 10.1016/S0140-6736(19)32989-7.
2. Buchman TG et al. Sepsis Among Medicare Beneficiaries: 1. The Burdens of Sepsis, 2012-2018. *Crit Care Med* 2020; doi: 10.1097/CCM.0000000000004224.
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4. SENTRY public database, JMI Laboratories, https://sentry-mvp.jmilabs.com/projects/2/filters/new.
5. CLSI-M7 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 11th Edition.

METHODS

Organism Selection and Sample Preparation

- Gram-negative antimicrobials were tested across *Enterobacterales* spp. (Enterics) species (*Escherichia coli* (ECOL), *Klebsiella pneumoniae* (KLPN)), as well as Non-fermenter (NF) species *Pseudomonas aeruginosa* (PSAR), and *Acinetobacter baumannii* (ABAU).
- Isolates were selected based on BMD MICs to cover desired reportable ranges.
- Higher fractions of on-scale and resistant isolates were chosen for this study compared to clinical distributions[4] (Figure 2)
- Isolates were seeded into blood culture bottles containing 10 mL of human donor blood and were incubated on a blood culture system until they flagged positive.

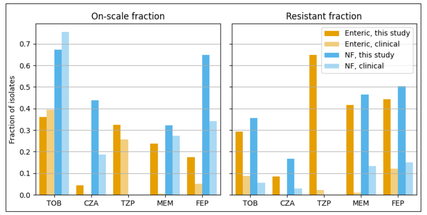
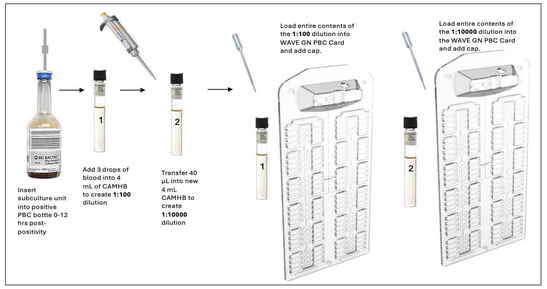


Figure 2. Fraction of isolates tested that were on-scale and resistant by BMD for select antimicrobials

Accelerate WAVE™ System* Testing



- ~2-min of pre-analytical steps (Figure 3) were performed on the PBC sample to create 2 sample dilutions and inoculate 2 cards.
- This 2-dilution approach minimizes the inoculum effect risk which could otherwise lead to potential inaccurate MIC results being reported.
- Prepared cards were then loaded into the Accelerate WAVE™ system*.

Figure 3. Pre-analytical ~2 min workflow for PBC sample

BMD Reference Testing

- PBC samples were sub-cultured to perform parallel reference BMD testing.
- The BMD panels were inoculated following CLSI guidance[5] in triplicate to obtain a modal BMD MIC.

Accelerate WAVE™ System Algorithm Development & Performance Analysis

- MIC algorithms / models were developed using a training component of the study data.
- MIC algorithms / models were then applied to new test data sets not used for algorithm training.
- MICs generated for the new test data sets were compared to BMD results to calculate essential agreement (EA)

RESULTS

- Each isolate tested generated a growth curve which was used to evaluate the differences in the growth response at each antimicrobial concentration. These growth curves, along with morphological and other complex responses, where applicable, were used to generate MIC results.
- Figure 4 shows an example set of growth curves of an *E. coli* isolate with a BMD MIC of 1 for cefepime.

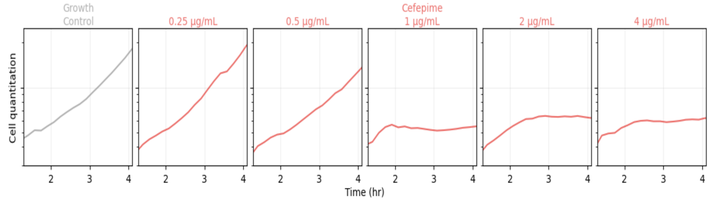


Figure 4. E. coli – cefepime (MIC=1) growth response

- The overall EA for each antibiotic class was above 90% (Table 1).

		AMK	GEN	TOB	AMC	SAM	CZA	CLT	TZP	MEM	CFZ	CXM	CAZ	CRO	FEP	CIP	LVX	ATM	AMP	SXT
ECOL	EA	88.7%	97.9%	96.7%	92.8%	93.4%	98.3%	93.2%	91.7%	92.0%	94.9%	91.1%	95.7%	96.0%	95.1%	96.1%	98.0%	95.7%	98.9%	97.5%
	on-scale	77.4%	20.6%	37.4%	80.4%	52.5%	0.0%	15.3%	32.1%	2.0%	36.4%	26.6%	20.3%	4.8%	12.6%	22.1%	15.2%	13.8%	6.4%	0.8%
	"R"	6.5%	25.8%	25.3%	33.0%	68.0%	5.0%	9.3%	45.9%	10.0%	65.7%	62.1%	39.1%	50.0%	36.9%	62.3%	55.6%	40.5%	84.0%	60.8%
KLPN	EA	96.2%	99.1%	97.1%	92.4%	95.0%	95.5%	91.8%	94.3%	90.2%		92.7%	90.7%	96.4%	90.3%	94.3%	96.1%	96.1%		93.6%
	on-scale	41.00%	11.9%	35.2%	46.2%	45.3%	4.5%	11.9%	43.8%	9.8%		10.2%	24.0%	6.4%	16.9%	20.7%	29.1%	10.1%		5.7%
	"R"	7.7%	26.6%	29.5%	41.2%	66.9%	3.4%	27.6%	39.0%	12.2%		67.2%	57.3%	60.7%	40.3%	59.8%	41.7%	55.0%		56.4%
ABAU	EA	95.5%				96.3%				100.0%			91.2%							
	on-scale	13.6%				59.3%				35.7%			55.9%							
	"R"	22.7%				11.1%				17.9%			44.1%							
PSAR	EA	94.9%		100.0%			94.1%	100.0%	89.8%	100.0%			90.0%		90.9%	95.1%	94.7%	93.5%		
	on-scale	33.3%		71.4%			44.1%	23.1%	65.0%	28.2%			30.0%		66.7%	29.3%	39.5%	61.3%		
	"R"	15.4%		31.0%			14.7%	12.8%	27.9%	48.7%			53.3%		54.5%	58.5%	63.2%	45.2%		
ALL GN	EA	93.5%	98.5%	97.5%	92.6%	94.4%	96.2%	93.5%	91.4%	94.9%	94.9%	92.0%	92.3%	96.2%	92.3%	95.1%	96.7%	95.7%	98.9%	95.4%
	on-scale	47.8%	16.0%	42.4%	61.6%	49.7%	10.4%	14.8%	52.0%	17.4%	16.5%	36.4%	18.0%	28.8%	5.7%	21.5%	22.9%	25.0%	17.4%	6.4%
	"R"	10.4%	26.2%	28.2%	37.5%	62.2%	6.0%	18.2%	50.7%	17.4%	21.5%	65.7%	64.8%	48.6%	55.7%	40.8%	60.5%	50.8%	47.8%	84.0%

Table 1. Essential agreement (EA) for each combination with percent on-scale isolates and resistant isolates tested (R).

- The average time to MIC results for the Gram-negative organisms tested in this study was 4 hours with a range of 3.0 to 4.7 hours across all antibiotics.

CONCLUSIONS

- This development study demonstrates the Accelerate WAVE™ system's* potential to report MIC results meeting essential agreement requirements for ECOL, KLPN, ABAU, and PSAR in an average of 4 hours directly from positive blood cultures.

Product under development and not available for sale. Subject to regulatory review and clearance.