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BRIEF REPORT

Day at the Races: Comparing BioFire FilmArray Blood Culture ID Panels With Verigene Blood Culture Panel in Gram-Negative Bloodstream Infections Using DOOR-MAT Analysis

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Three rapid diagnostic test panels (Verigene BC-GN, BioFire BCID, and BCID 2 [RUO]) were compared using the Desirability of Outcome Ranking Management of Antimicrobial Therapy (DOOR-MAT) to evaluate potential downstream antimicrobial prescribing decisions resulting from the panels' different organism and resistance detection. BioFire BCID 2 (RUO) had the best mean DOOR-MAT scores.

Keywords. bloodstream infections; gram-negative; rapid diagnostic testing.

Rapid diagnostic tests (RDTs) are commonly used for the management of bloodstream infections (BSIs) and have demonstrated the ability to streamline antimicrobial therapy hours to days sooner than traditional methods [1–5]. Clinical data to guide optimal implementation of RDTs for gram-negative BSIs, however, are scarce [1, 3, 6, 7]. This is likely secondary to the greater number and diversity of gram-negative pathogens and their antimicrobial resistance mechanisms. This issue of optimal use of gram-negative RDTs is further compounded by the growing number of commercially available platforms that detect a variety of different organisms and genetic markers of resistance.

Comparisons of commercially available RDT platforms are limited to in vitro assessment of sensitivity and specificity of organisms common to both panels, which provide little insight into their impact on clinical decision making [8, 9]. The ability to compare the potential downstream antimicrobial choice based on detection of organisms and resistance from different RDTs panels would greatly assist clinical microbiology laboratories and antimicrobial stewardship programs in choice of platform. To help overcome this limitation, the Antibiotic Resistance Leadership Group developed the Desirability of Outcome Ranking Management of Antimicrobial Therapy (DOOR-MAT) framework for objective, quantitative evaluation of antimicrobial prescribing decisions, which can be applied as a function of RDT and final phenotypic susceptibility results [10]. Through use of DOOR-MAT, institutions can better determine which RDTs to implement based on local infectious diseases epidemiology and prescribing patterns. The objective of the current study is to compare theoretical antimicrobial prescribing based on 3 RDT panels in gram-negative BSIs using the DOOR-MAT framework.

METHODS

This was a retrospective proof-in-concept study conducted at the University of Maryland Medical System from August 2018 to August 2019. Blood cultures from adult patients with gram-negative organisms identified via Gram stain were eligible for inclusion. Three RDT panels were compared: Verigene Blood Culture Gram-Negative (BC-GN; Luminex Corporation, Austin, TX), the BioFire FilmArray Blood Culture ID (BCID) Panel (BioFire Diagnostics, Salt Lake City, UT), and the BioFire BCID 2 Panel (Research Use Only [RUO]; BioFire Diagnostics). A comparison of organisms and resistance determinants detected is provided in Supplementary Table 1. The Verigene BC-GN microarray panel was performed as part of routine clinical practice during this study. BioFire FilmArray BCID and BCID 2 were tested on leftover blood samples that were frozen at −80°C after routine clinical testing; these results were not made available to providers. We collected demographic and clinical data, including source of BSI and intensive care unit (ICU) admission, from the electronic medical record for each included patient. Final organism identification and phenotypic susceptibility results were based on VITEK MS/VITEK 2 automated susceptibility testing (AST; bioMérieux, Inc, Durham, NC).

For the in vitro comparison of panels, results of Verigene BC-GN, BioFire FilmArray BCID, and BioFire BCID 2 were each compared with the final organism identification and

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phenotypic susceptibility reported from VITEK MS/VITEK 2. Positive percent agreement (PPA) between each panel and VITEK MS/VITEK 2 was calculated for respective on-panel targets [11].

To evaluate potential differences in antimicrobial prescribing based on RDT panel results, DOOR-MAT matrices were developed a priori for organisms that were on at least 1 panel, including the following: *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Escherichia coli*, and *Klebsiella* spp., and potential AmpC-producing *Enterobacterales* (*Enterobacter* spp., *Citrobacter* spp., *Serratia marcescens, Morganella morganii*). To create the DOOR-MAT matrix, first, antimicrobials commonly used at our institution were selected and ranked on their known spectrums of activity for each organism, from most narrow to most broad. Then we determined common phenotypic resistance profiles that would result from AST. These ranged from being susceptible to all antimicrobials to resistant to all but agents of last resort. These attributes of antimicrobial spectrum and resistance profile were cross-referenced to create the DOOR-MAT matrix. The frameworks were then associated with a partial credit scoring system that assigns zero points to inactive/ineffective therapy and 100 points to optimal therapy. An example DOOR-MAT matrix, partial credit scoring system, and theoretical clinical scenario scores are provided in Figure 1.

An infectious disease–trained clinician reviewed RDT results provided from each panel. Theoretical antimicrobial therapy decisions were made using those results in conjunction with relevant patient variables, such as source of infection, ICU admission, antimicrobial allergies, along with local infectious diseases epidemiology through review of institutional antibiogram data. Final phenotypic susceptibility results were not provided at this stage. These antimicrobial therapy decisions were compared against final organism identification and phenotypic susceptibility information using the previously defined DOOR-MAT framework and partial credit scoring system.

For each RDT panel, scores were analyzed as means with standard deviations (SDs) because nonparametric analysis would revert to ranks and negate the partial credit scoring system [12]. Comparisons were made using analysis of variance with repeated-measures analysis, followed by paired *t* test with modified Bonferroni correction in Microsoft Excel (Microsoft Corporation, Redmond, WA) and SAS (version 9.4; SAS Institute, Cary, NC).

RESULTS

From the 103 blood culture samples collected, 108 gram-negative organisms were identified. The most common organisms were *E. coli* (32, 29.6%), *Klebsiella pneumoniae* (19, 17.6%), and *S. marcescens* (10, 9.3%). Certain organisms were not on any of the panels and were thus excluded from determination of PPA for all panels: *Pasteurella multocida* (2), *Burkholderia* spp. (1), *Paenibacillus lautus* (1), *Prevotella intermedia* (1), *Achromobacter* spp. (2), *Pseudomonas pseudoalcaligenes* (1), and *Psychrobacter* spp. (1). The Verigene BC-GN panel does not include *B. fragilis* (1), *S. marcescens* (10), and *S. maltophilia* (4), so they were excluded for the Verigene calculation. Among included organisms, the Verigene BC-GN panel failed to identify 1 *K. pneumoniae* for an overall PPA of 98.8% (81/82). The BioFire FilmArray BCID panel does not include *S. maltophilia* (4), *Bacteroides fragilis* (1), *Citrobacter* spp. (1), or *Acinetobacter junii* (1), so those were excluded. BioFire FilmArray BCID misidentified 1 *E. coli* and missed 1 *Acinetobacter baumannii* for PPA of 97.8% (90/92). The BioFire BCID 2 had a PPA of 96.9% (94/97), missing 1 *E. coli*, 1 *S. maltophilia*, and 1 *E. cloacae* complex. Of note, among the 25 organisms not on the Verigene BC-GN panel, BioFire BCID 2 detected 15 (60%). Additionally, among the 16 organisms not on the BioFire BCID panel, the BioFire BCID 2 detected 6 (24%). Verigene BC-GN and BioFire BCID 2 both identified 6 CTX-M; this was the only genetic resistance detected.

All 103 patients were included in the final DOOR-MAT analysis. The most common source of BSI was urinary (31.1%), followed by unknown (23.3%). Blood cultures were obtained in the ICU in 44 (42.7%) patients and 70 (67.9%) had an infectious disease consult at the time of blood culture collection. Patients were commonly admitted to shock trauma (17, 16.7%) or oncology (16, 15.7%). The most common empiric gram-negative antimicrobial was piperacillin-tazobactam (51, 49.5%). The mean DOOR-MAT score for Verigene BC-GN was 83.8 (SD, ±25.7) compared with 59.9 (SD, ±33.7) for BioFire BCID and 89.7 (SD,±24.7) for BioFire BCID 2. Overall, there was a significant difference in mean DOOR-MAT scores ($P < .0001$) across the 3 platforms. The mean DOOR-MAT score was higher for BioFire BCID 2 than both BioFire FilmArray BCID ($P < .0001$) and Verigene BC-GN ($P = .07$).

DISCUSSION

All 3 RDTs had high in vitro agreement for on-panel targets with final identification through VITEK MS. When compared with the Verigene BC-GN panel, the higher mean DOOR-MAT score for BioFire BCID2 can largely be attributed to the detection of an expanded panel organism. When compared with BioFire BCID, the significantly expanded detection of resistance determinants allows not only for prompt escalation in the presence of CTX-M production but also allows the potential to de-escalate in the absence of CTX-M [13]. The addition of *S. maltophilia* to the BioFire BCID 2 panel was also beneficial in our patient population, which consists of many immune-compromised patients.

The use of DOOR-MAT to compare potential antimicrobial prescribing decisions remains a novel methodology. Our study demonstrated a potential application of DOOR-MAT to assist

Clinical Scenario

41 year-old female on the transplant medical floor (not ICU), urinary source of infection. No known drug allergies or prior MDROs. Previous antibiotic exposure during hospitalization includes vancomycin and cefazolin.

Step 1: Respective RDT Results

Verigene BC	BioFire BCID	BioFire BCID 2
E. coli CTX -M (–)	*E. Coli*	*E. coli* CTX -M (–)

Step 2: Antimicrobial Choice

Ceftriaxone	Piperacillin-tazobactam	Ceftriaxone

Step 3: Final Organism ID &AST

E. coli (CFZ S, CRO S, TZP S, FEP S, MEM S)

Step 4: Reference DOOR-MAT Matrix and Partial Credit Score

Antimicrobial Spectrum	Phenotypic Resistance Profiles				
	SSSSS	RSSSS	RRSSS	RRRSS	RRRRS
Optimal: cefazolin, ampicillin/sulbactam	S	R	R	R	R
Intermediate 1: ceftriaxone	S	S	R	R	R
Intermediate 2: piperacillin/tazobactam, cefepime	S	S	S	R	R
Broad: meropenem, ertapenem	S	S	S	S	R
Last Resort: ceftazidime/avibactam, meropenem/vabrobactam	S	S	S	S	S

Partial Credit Scoring Scheme	
Antimicrobial Desirability	Score
Optimal	100
Slight Over Treatment	50
Moderate Over Treatment	25
Inactive/Ineffective	0

DOOR-MAT Spectrum and Partial Credit Score

Verigene BC	BioFire BCID	BioFire BCID 2
Optimal	Slight over-treatment	Optimal
100	50	100

Step 5: For reach RDT panel, average (SD) scores across patients (not pictured)

Figure 1. Example and potential clinical application of DOOR-MAT matrix. Abbreviations: CFZ, cefazolin; CRO, ceftriaxone; DOOR-MAT, Desirability of Outcome Ranking Management of Antimicrobial Therapy; FEP, cefepime; ICU, intensive care unit; MEM, meropenem; MDRO, multi-drug-resistant organism; RDT, rapid diagnostic testing; TZP, piperacillin-tazobactam.

institutions with more robust comparisons of RDT platforms than available through in vitro analysis, while not having to commit to large-scale clinical trials. Its applications, such as inclusion in diagnostic trials, have not been fully explored. Additional validation and analysis can also be considered. The spectrum of activity and partial credit scoring could be validated through expert consensus, like the recently published *Staphylococcus aureus* bacteremia DOOR [14]. Analysts could additionally perform sensitivity analysis on different scoring systems and model how RDTs compare under these different systems. This brief report serves as an introduction to a potential application of DOOR-MAT, and these considerations are beyond the current scope.

This study is limited by the theoretical nature of these comparisons. The DOOR-MAT framework does not incorporate any considerations for timing of therapy changes. Also, although we have attempted to address the complexity of patient presentation on antimicrobial decision making, scoring is largely reflective of final organism characteristics.

The DOOR-MAT framework allows for a quantitative, yet flexible framework to consider the impact of diagnostics on antimicrobial decisions. These findings highlight the importance of local infectious epidemiology with regard to antimicrobial decision making in gram-negative BSIs. The use of DOOR-MAT has the potential for efficient and meaningful comparisons of RDT panels beyond in vitro sensitivity and specificity.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. K. C. C. and J. K. J. have received study supplies from BioFire Diagnostics and GenMark Diagnostics and served as speakers for GenMark Diagnostics. S. E. reports Data and Safety Monitoring Board fees from Takeda/Millennium, Pfizer, Roche, Novartis, National Institutes of Health, Austrian Breast & Colorectal Cancer Study Group/Breast International Group, the Alliance Foundation Trials, Vir, Shire, Alexion, Tracon, Advantagene, Roche, Rakuten, Duke University, University of Pennsylvania, Takeda, Nuvelution, Abbvie, Clover, FHI Clinical, Lung Biotech, Gilead, and SAB Biopharm; Think Tank fees from ACTTION, Genentech, Amgen, Teva, Cardinal Health, Stryker, Atricure, Roivant, Neovasc, Nobel Pharma, and Horizon; Board of Directors' fees from American Statistical Association and Society for Clinical Trials; teaching fees from American Statistical Association, the Food and Drug Administration (FDA), Osaka University, and National Cerebral and Cardiovascular Center of Japan; travel fees from American Statistical Association and Society for Clinical Trials; speaking fees from the Society for Clinical Trials, Deming Conference, Antimicrobial Resistance and Stewardship Conference; advisor fees from FDA, AstraZeneca, Microbiotix, BENEFIT, Council for International Organizations of Medical Sciences, and SVB LEERINK; Editor-in-Chief fees from Statistical Communications in Infectious Diseases (DeGruyter); book royalty fees from Taylor and Francis; and funding as Director of the Statistical and Data Management Center for the Antibiotic Resistance Leadership Group funded by the National Institute of Allergy and Infectious Diseases, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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