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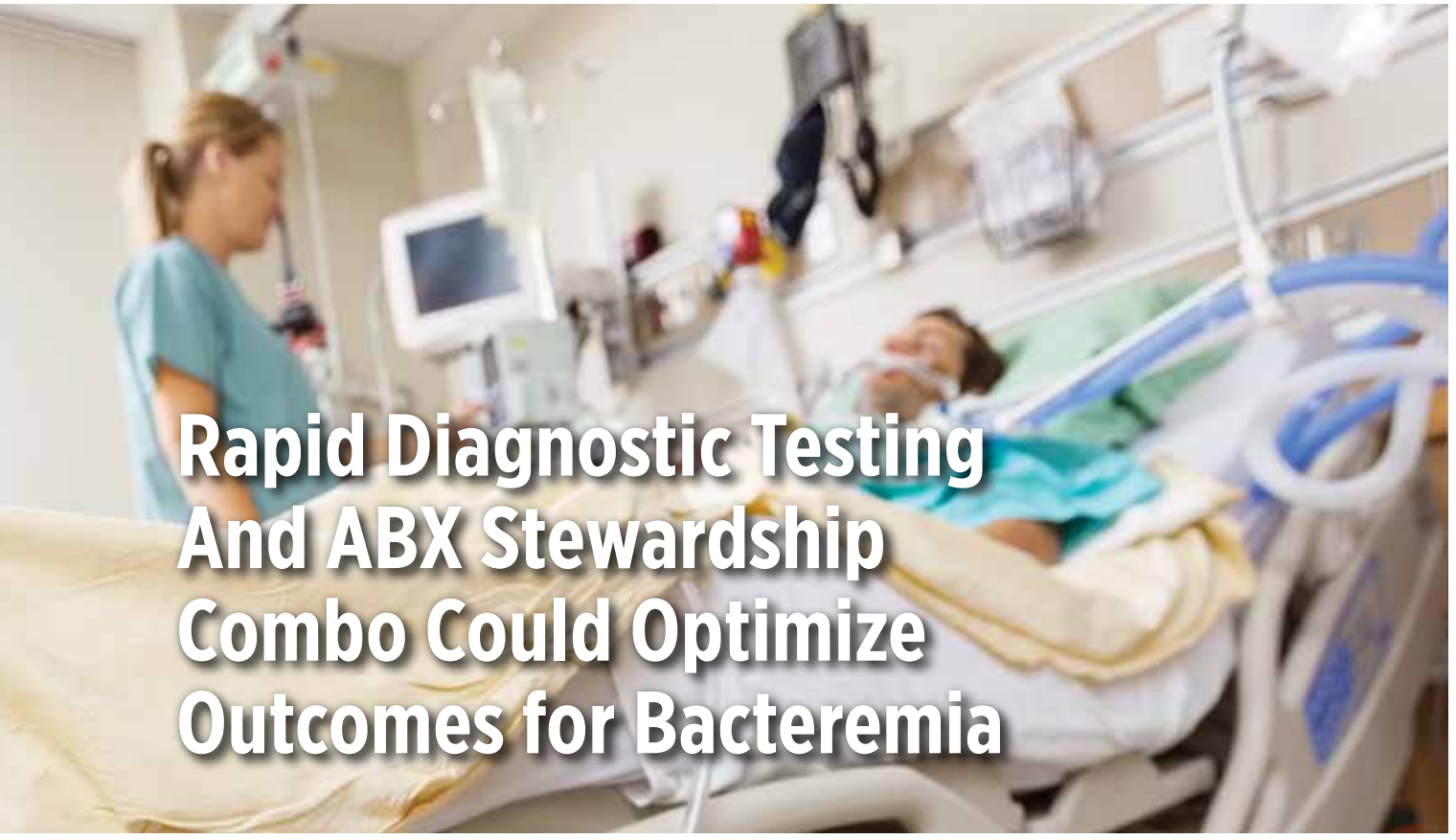

Rapid Diagnostic Testing And ABX Stewardship Combo Could Optimize Outcomes for Bacteremia

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The primary goal of antimicrobial stewardship programs (ASPs) should be to optimize patients' clinical outcomes, and rapid diagnostic testing (RDT) helps achieve this goal more so than any other intervention. Timbrook et al established the efficacy of molecular RDT with ASP intervention in the care of patients with bloodstream infections in a meta-analysis, and the Society of Infectious Diseases Pharmacists recently published a position statement on the role of ASPs in the use of RDT in the acute care setting.[1,2] Despite the known efficacy of this strategy, barriers to implementation exist, including cost, lack of C-suite support, and an incomplete understanding of how best to implement and optimize use of RDT with ASP intervention.

Barriers to RDT Implementation

The most commonly cited barrier to implementation of RDT is cost. Pliakos et al recently evaluated the cost-effectiveness of competing strategies for diagnosing and treating bloodstream infections with or without ASP intervention.[3] Overall, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) with ASP intervention was the most cost-effective strategy compared with conventional microbiology without an ASP, saving $29,205 and preventing 1 death in every 14 patients with a suspected bloodstream infection. RDT with ASP intervention had an 80% chance of being cost-effective in probabilistic models, compared with a 41% chance with RDT without ASP intervention.

These results add to previous clinical efficacy studies and confirm that optimal outcomes for patients with bloodstream infections are achieved by using RDT plus ASP intervention and that this strategy is more cost-effective than conventional microbiology with or without ASP. In fact, use of conventional laboratory methods with an ASP was not a cost-effective strategy in this analysis.

When the wealth of clinical data and this comprehensive cost analysis are considered together, it is clear that RDT plus ASP intervention should be the standard of care for all patients with bloodstream infections. As further data become available, a more granular analysis of specific molecular RDT in combination with ASPs and their cost-effectiveness will be valuable to clinicians. Additionally, clinical data on new direct-from-blood assays, such as the T2Candida and T2Bacteria platforms (T2 Biosystems), and rapid phenotypic systems, such as the PhenoTest BC Kit (Accelerate Diagnostics), are needed to establish whether they are cost-effective strategies.

In addition to cost, a lack of C-suite support and a lack of understanding of how best to implement and optimize RDT often are cited as barriers to their uptake. My colleagues and I recently summarized these barriers and provided strategies for how an ASP may justify the addition of an RDT to its program and optimize its use.[4] We discuss ways in which the RDT can be justified through cost savings and by using the RDT to meet some of the CDC Core Elements for antimicrobial stewardship (**Table**). Considering the mandate for ASPs across all US acute care hospitals accredited by the Joint Commission, we provide approaches for clinicians not trained in infectious diseases to help them justify adding an RDT to their ASP interventions for patients with bloodstream infections and guidance on how to optimize RDT use (eg, performing good diagnostic stewardship and appropriate metrics to measure related to RDT outcomes).

Novel Application of RDT

Although ample data exist to establish RDT plus ASP intervention as the standard of care for patients with bloodstream infections, new studies evaluating novel techniques or applying RDT and ASP intervention in new settings are continually being published to help us further refine how and where exactly RDT can be used to optimize patient care.

Pogue et al recently addressed an important issue facing ASPs that use molecular RDT with genotypic markers of resistance: what to do in the case of genotypic:phenotypic discordance in susceptibilities for gram-negative pathogens.[5] The authors examined 1,046 gram-negative bloodstream isolates for which the Verigene gram-negative blood culture test (Luminex) did not detect any resistance markers; they found that the negative predictive values exceeded 90% for bug–drug combinations, including Enterobacteriaceae. The results were less reliable for *Pseudomonas aeruginosa* because of the more complex resistance mechanisms of this pathogen. Their work gives clinicians further confidence in the reliability of molecular RDT and provides guidance for individual institutions to perform their own analysis comparing their phenotypic antibiogram with one predicted by genotypic markers detected by the Verigene system.

Bookstaver et al evaluated the effect of sequential introduction of MALDI-TOF MS followed by the FilmArray blood culture identification panel (BCID) (bioMérieux) added to an existing robust ASP for patients with gram-negative bloodstream infections.[6] Used together, RDT and ASPs resulted in significant reductions

TABLE. Justifying RDT to Hospital Administration Using CDC Core Elements

Core Element	How RDT May Affect or Fulfill Core Element
Leadership Support • Financial support	• Financial backing required from administration for initial fixed and variable costs associated with RDT implementation
Accountability • Physician leader responsible for ASP	• Accountable for RDT implementation and outcomes • Prioritize use of RDT as daily ASP activities • Advocate resource use to appropriately implement, track, and report results among appropriate stakeholders
Drug Expertise • Pharmacist leader to improve antibiotic utilization	• Performs daily ASP interventions • Helps streamline process for antibiotic administration from pharmacy in a timely manner • Helps collect, analyze, and report data
Actions • Implement specific intervention to improve antibiotic use	• Conduct prospective audit and feedback on positive blood cultures • Considered advanced activity per Playbook as diagnosis- and infection-specific intervention • Align with local needs • Measure outcomes
Tracking/Monitoring • Process measures • Monitoring compliance with specific intervention in place	• Considered intermediate activity to monitor a specific intervention per Playbook • RDT provides a tangible outcome to monitor and is targeted and clinically significant • BSI infrequent enough to not require arduous data collection • Outcomes include mortality, length of stay, time to appropriate therapy, and time to optimal therapy
Reporting • Share outcomes with key stakeholders	• Outcomes shared with key stakeholders • C-suite: confirms continual ASP support • ASP: demonstrate follow-through for core element accountability • Pharmacy director uses reporting as demonstration of pharmacy activities and impact • Other stakeholders: various subgroups within hospital that may benefit (eg, ED and ICU)
Education • For clinicians and providers	• Provided at RDT rollout to improve acceptance rates • RDT data may be provided to improve confidence in ASP when making recommendations

ASP, antimicrobial stewardship program; **BSI,** bloodstream infection; **ED,** emergency department; **mRDT,** molecular rapid diagnostic test; **RDT,** rapid diagnostic testing

in median time to antimicrobial de-escalation from combination therapy, antipseudomonal beta-lactams, and carbapenems compared with ASPs without RDT. Compared with MALDI-TOF MS plus an ASP alone, these strategies combined with the FilmArray BCID resulted in further significant reductions in median time to de-escalation of antipseudomonal beta-lactams and carbapenems.

Of note, this study touches on 2 important points often cited as uncertainties in the implementation of RDT: First, does adding RDT to a well-established ASP have a beneficial effect? Second, is all RDT created equal, or do we need to use a test that identifies resistance markers? This study along with previous data in this area[7] answers both of these questions with a resounding yes.

Finally, an interesting study by Avdic et al took a novel approach to teasing out the effect of implementing RDT with or without ASP intervention.[8] The authors compared time to antibiotic optimization and clinical outcomes during 3 periods: a baseline period before implementation of the Verigene gram-positive blood culture (BC-GP) assay (Luminex); an intervention period, during which investigators used a BC-GP assay plus ASP intervention; and a post-intervention period, during which they used a BC-GP assay without ASP intervention. Each period lasted for 7 months, and the primary outcome was time to optimal therapy, defined as time from the positive Gram stain to time of initiation of the narrowest spectrum agent possible. Of note, patients already on optimal therapy were excluded from this analysis.

The authors found that for patients with methicillin-sensitive *Staphylococcus aureus* bacteremia, time to optimal therapy was significantly shorter in the intervention (median time, 17 hours) and post-intervention arms (median time, 17 hours) compared with the baseline arm without RDT or an ASP (median time, 50 hours). For patients with *Enterococcus faecalis* bacteremia, significant differences were found between patients in the intervention arm compared with the baseline arm, but not for the post-intervention (RDT-only) arm. In the adjusted analysis, both RDT plus an ASP and RDT alone significantly reduced the time to optimal therapy for patients who otherwise would have experienced more than a 24-hour delay in time to optimal therapy without intervention. No differences in time to effective therapy or clinical outcomes were observed. These findings are novel and important for clinicians using RDT because they suggest that after RDT is implemented with ASP interventions, ASP interventions potentially can be discontinued once clinicians are educated and become comfortable with RDT.

Up-and-Coming Rapid Diagnostic Tests

More data continue to be published about the potential impact on patient outcomes when newly approved RDT systems, such as the PhenoTest BC Kit[9] and T2Candida assay,[10] are combined with an ASP. These systems are particularly exciting, as they allow clinicians to shorten the timeline from identification of suspected infection to administration of effective antimicrobial therapy, even compared with the timelines associated

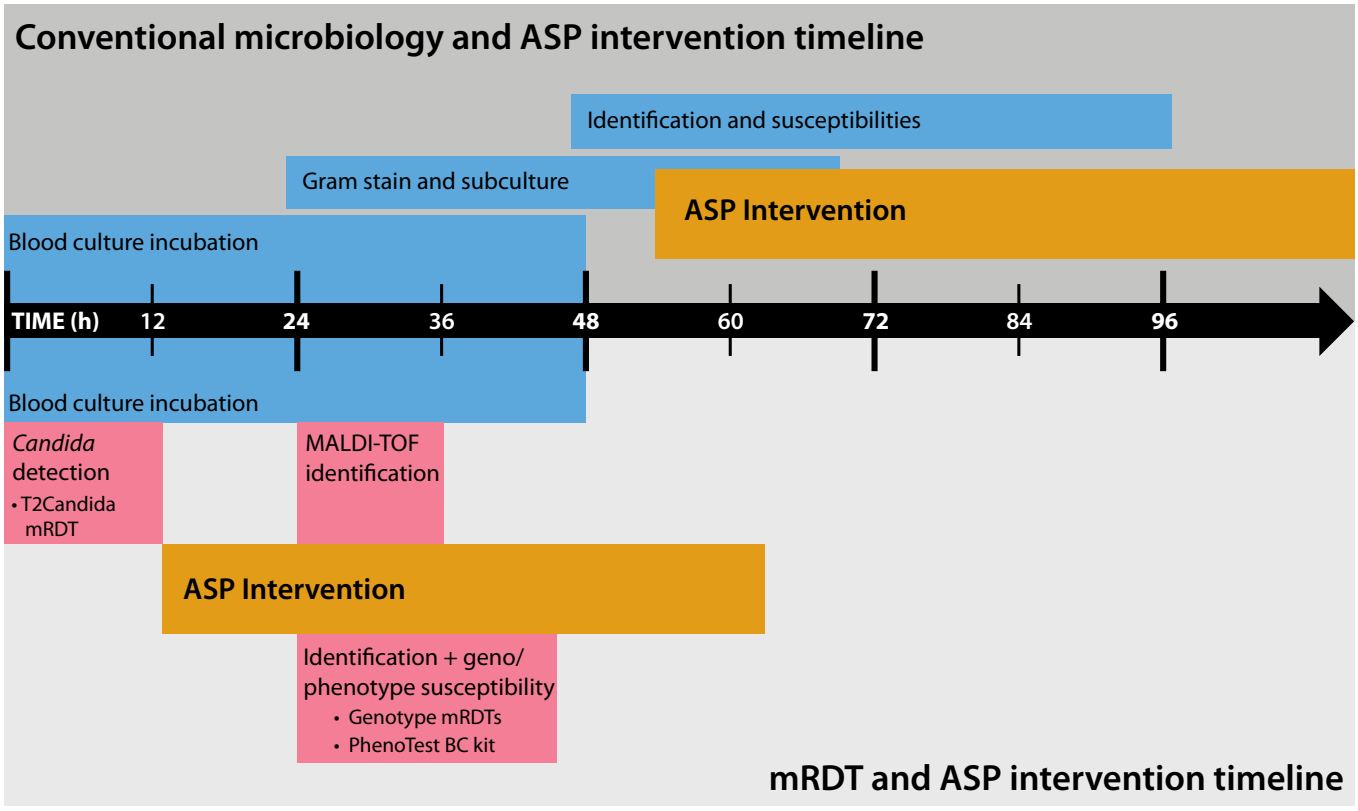

FIGURE. Impact of mRDT on time to organism identification, susceptibility, and ASP intervention compared with conventional microbiology.

ASP, antimicrobial stewardship program; **MALDI-TOF,** matrix-assisted laser desorption/ionization time-of-flight; **mRDT,** molecular rapid diagnostic testing

America spent $10.7 billion on antibiotics in 2009; $3.5 billion among hospitalized patients.

Source: CDC

with existing RDT (Figure). These results appear promising and should pave the way for future larger studies needed to solidify the place in therapy for these systems.

The T2Bacteria Panel, which uses the previously discussed T2 magnetic resonance technology on the T2Dx platform (T2 Biosystems), was cleared by the FDA in May 2018 for the direct detection of bacterial species in human whole blood specimens.[11] This gives it the distinction of being the first FDA-cleared direct-from-blood bacterial assay approved in the United States. The assay is fully automated and automatically completes all the procedural steps required for analysis after the blood sample is loaded. The panel is cleared for *S. aureus, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae*, and *P. aeruginosa*, but a study by De Angelis showed that it also can detect *Acinetobacter baumannii*, and has the capability of yielding a positive or negative result for 1 or more of 6 bacterial species (*S. aureus, E. faecium, E. coli, K. pneumoniae, P. aeruginosa,* and *A. baumannii*), with a limit of detection as low as 1 CFU/mL and sensitivity and specificity of 89.5% and 98.4%, respectively, for patients with clinical symptoms of infection.[12] They found the mean time to species identification was 5.5±1.4 hours. Given the sensitivity of the T2Bacteria assay, it may be particularly useful in patients receiving antimicrobial therapy at the time of culture (conventional blood cultures may be falsely negative in such patients), although the small number of species detected and the lack of resistance marker detection will limit its overall clinical utility.

Finally, looking into the pipeline of RDT, the ePlex system (GenMark Diagnostics) is an exciting technology undergoing phase 3 trials. The system's BCID panels for gram-positive, gram-negative, and fungal organisms include an impressive number of genus, species, and resistance marker detections.[13] Additionally, both the gram-positive and gram-negative BCID panels have a unique pantarget assay for *Candida* species and the opposite panel species; thus, a gram-positive pathogen would still be identified as such if it were present in a blood culture sample placed into the gram-negative BCID panel based on the initial Gram stain performed in the laboratory. The ePlex system also will attempt to solve previous frustrations with RDT by allowing bidirectional connectivity with the laboratory information system; the system requires less than 2 minutes of hands-on time, and the time from sample to result is approximately 1.5 hours.

Conclusion

Further studies are needed to confirm the value of RDT in niche patient populations, in infections other than bacteremia, and in nonacademic institutional settings, but care of the vast majority of patients afflicted with bloodstream infections should involve use of RDT with ASP intervention. This combined intervention has been shown to reduce mortality and is more cost-effective than traditional microbiologic techniques as well as RDT without ASP. As ASPs are mandated in US hospitals, clinicians and pharmacists who do not have infectious disease training should use the available evidence to best implement their RDT. Informed decisions about the institution-specific utility of available RDT should be made by a multidisciplinary team and be based on facility-derived baseline data compared with post-implementation data. As RDT technologies continue to advance and provide more valuable information sooner, ASPs with RDT should continue to evaluate available clinical and economic effectiveness data to ensure clinicians and pharmacists are providing optimal care to their patients with bloodstream infections.

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