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# The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis

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*Background.* Previous reports on molecular rapid diagnostic testing (mRDT) do not consistently demonstrate improved clinical outcomes in bloodstream infections (BSIs). This meta-analysis seeks to evaluate the impact of mRDT in improving clinical outcomes in BSIs.

*Methods.* We searched PubMed, CINAHL, Web of Science, and EMBASE through May 2016 for BSI studies comparing clinical outcomes between mRDT and conventional microbiology methods.

*Results.* Thirty-one studies were included with 5920 patients. The mortality risk was significantly lower with mRDT than with conventional microbiology methods (odds ratio [OR], 0.66; 95% confidence interval [CI], .54–.80), yielding a number needed to treat of 20. The mortality risk was slightly lower with mRDT in studies with antimicrobial stewardship programs (ASPs) (OR, 0.64; 95% CI, .51–.79), and non-ASP studies failed to demonstrate a significant decrease in mortality risk (0.72; .46–1.12). Significant decreases in mortality risk were observed with both gram-positive (OR, 0.73; 95% CI, .55–.97) and gram-negative organisms (0.51; .33–.78) but not yeast (0.90; .49–1.67). Time to effective therapy decreased by a weighted mean difference of −5.03 hours (95% CI, −8.60 to −1.45 hours), and length of stay decreased by −2.48 days (−3.90 to −1.06 days).

*Conclusions.* For BSIs, mRDT was associated with significant decreases in mortality risk in the presence of a ASP, but not in its absence. mRDT also decreased the time to effective therapy and the length of stay. mRDT should be considered as part of the standard of care in patients with BSIs.

*Keywords.* rapid diagnostic tests; bloodstream infections; meta-analysis; antimicrobial stewardship.

Bloodstream infections (BSIs) are associated with significant morbidity and mortality risks and significantly increased length of stay (LOS) [1, 2]. Delayed administration of effective antibiotics increases the mortality risk and therefore correct selection of an antibiotic regimen early in the treatment process is paramount [3, 4]. Delayed identification of the causative organism and culture susceptibilities may often be responsible for delays in optimal antimicrobial therapy. Molecular rapid diagnostic testing (mRDT), which includes tests such as polymerase chain reaction (PCR), matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry, and peptide nucleic acid fluorescent in situ hybridization (PNA-FISH), has improved on conventional microbiologic methods, reducing time to organism identification, optimizing antimicrobial therapy, and subsequently improving clinical outcomes, including mortality rates [5].

Advancement of RDT is included among 5 overarching goals from the National Action Plan for Combating Antibiotic-Resistant

Bacteria [6]. In addition, the 2016 Infectious Diseases Society of America antimicrobial stewardship program (ASP) guidelines recommend the use of rapid diagnostic testing (RDT) with ASP support and intervention as an addition to conventional methods for blood specimens to improve clinical outcomes [7]. Widespread implementation of this technology has been limited owing to inadequate outcomes data and high costs [8]. A recent meta-analysis included evaluations of the clinical benefits of molecular and phenotypic RDT in BSIs but was limited by the time frame of the literature included, with the most recent study being published in 2012 [9]. In addition, the impact on LOS was not assessed, nor was the effect on mortality risk according to ASP presence. The objective of this systematic review and meta-analysis was to provide a comprehensive and up-to-date assessment of mRDT's effects on mortality risk, time to effective therapy, and LOS, when compared with conventional microbiology methods in patients with BSIs.

## METHODS

### Literature Search

We searched PubMed, CINAHL, Web of Science, and Embase from inception to 31 May 2016 for BSI studies in English comparing clinical outcomes between mRDT and conventional microbiology methods. We used the following search query:

(bacteremia or "bloodstream infection") *and* (spectrometry or "matrix assisted laser desorption/ionization" or MALDI-TOF or microarray or PCR or "nucleic acid" or PNA or molecular or "polymerase chain reaction") *and* ("length of stay" or mortality or morbidity or diagnosis or outcome). Two authors (T. T. T. and J. B. M.) searched the literature and performed article selection independently. Differences were resolved through consensus involving a third author (K. W. M.). The references for the included articles were searched manually to identify additional relevant studies. Unpublished studies were included through searching abstracts from IDWeek, the Interscience Conference on Antimicrobial Agents and Chemotherapy, and the European Congress of Clinical Microbiology and Infectious Diseases from 2007 to 2015, using the keywords "bacteremia" or "bloodstream infection."

### Study Selection

All studies evaluating the differences in clinical outcomes between mRDT, either for organism identification and/or resistance mechanism detection, and conventional methods in BSIs were eligible for inclusion. mRDT was defined as commercially available molecular tests that can provide results in ≤24 hours. Studies were included if results were reported for clinical outcomes of interest. Studies were excluded if they were non-English studies, if they evaluated infections with mycobacterial, viral, or parasitic organisms, or if they applied mRDT to negative blood cultures or direct blood specimens (eg, Septifast).

### Outcomes

Outcomes evaluated included overall mortality risk, mortality risk in studies with ASP, mortality risk by organism, time to effective therapy, and LOS. Mortality risk was defined as all-cause 30-day or in-hospital mortality risk. Organism types were grouped as gram positive, gram negative, yeast, or, if a combination of these, multiple. Time to effective therapy was defined as the time from either blood specimen collection or positive test result to a therapy with in vitro activity against the infecting organism. LOS was defined as total hospital LOS or LOS beginning with culture collection or positivity among either survivors or all patients within the study. Studies were classified as ASP studies if the authors reported infectious diseases physician or pharmacist review of antimicrobial selection based on culture or mRDT results.

### Quality Assessments

Assessments of quality were made by 2 authors (T. T. T. and J. B. M.) using the Newcastle-Ottawa Scale [10] for observational studies and the Risk of Bias tool for randomized controlled trials [11]. The Newcastle-Ottawa Scale evaluates for the selection of patients, comparability of patients, and assessment of outcomes. The Risk of Bias tool assess whether there is a low, high, or unclear level of bias based on 5 primary domains of bias in randomized controlled trials, including selection, performance, detection, attrition, and reporting bias [12]. Differences

in quality assessment between the 2 authors were resolved through consensus involving a third author (K. W. M.).

### Data Extraction and Analysis

All meta-analyses were performed using Review Manager software (The Cochrane Collaboration, version 5.3). Mortality outcomes were assessed using a random-effects model to estimate pooled odds ratios (ORs) and 95% confidence intervals (CIs) with weights as described by DerSimonian and Laird [13]. To express the effect of testing in clinical terms, the number needed to treat to prevent 1 death was calculated. The effect of mRDT on time to effective therapy and LOS was evaluated using a random-effects model and reported as weighted mean difference with 95% CI. Medians and interquartile ranges or ranges were converted to means and standard deviations according to Wan et al [14]. Publication bias was assessed using funnel plots and Egger's test. Heterogeneity between studies was evaluated with $I^2$ estimation and the Cochran Q test [12]. For heterogeneity testing, results were considered significant at $P < .10$, because the Q test has low power. Random-effects univariate meta-regressions were performed for covariates that had possible effects on an outcome and were reported in ≥10 studies, using the metaphor package in R software (R Foundation for Statistical Computing, version 3.2.3). This systematic literature review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1).

## RESULTS

The literature search resulted in 7273 studies meeting the keyword criteria (Figure 1). After removal of duplicates, titles and abstracts were reviewed for 5426 studies. Studies not related to our search were removed, yielding 40 studies for full text review. Full-text review identified 5 articles with data not relevant to our meta-analysis, 3 studies without clinical outcomes, 2 studies with mRDT in each comparison arm, and 2 studies that evaluated mRDT on blood specimens in septic patients without positive cultures. Review of the references of the included studies resulted in 4 additional studies being added to the meta-analysis. Data were extracted from 31 studies with 5920 patients, because 2 studies [15, 16] contained overlapping data.

Characteristics of the included studies are shown in Table 1. Only 6 studies (19.4%) [18, 21, 35, 37, 44, 46] were conducted outside the United States. The majority of studies included (26 of 31; 83.9%) were designed as pre- and postintervention quasi-experimental studies at mRDT initiation. Although most of the studies reporting study setting were academic medical centers, 2 of the included studies (6.5%) [20, 30] were from community hospitals. Among studies reporting patient population information, adult patients were the most common cohort studied (95.2%; 20 of 21). Gram-positive organisms were the most frequently reported BSI type included, occurring in
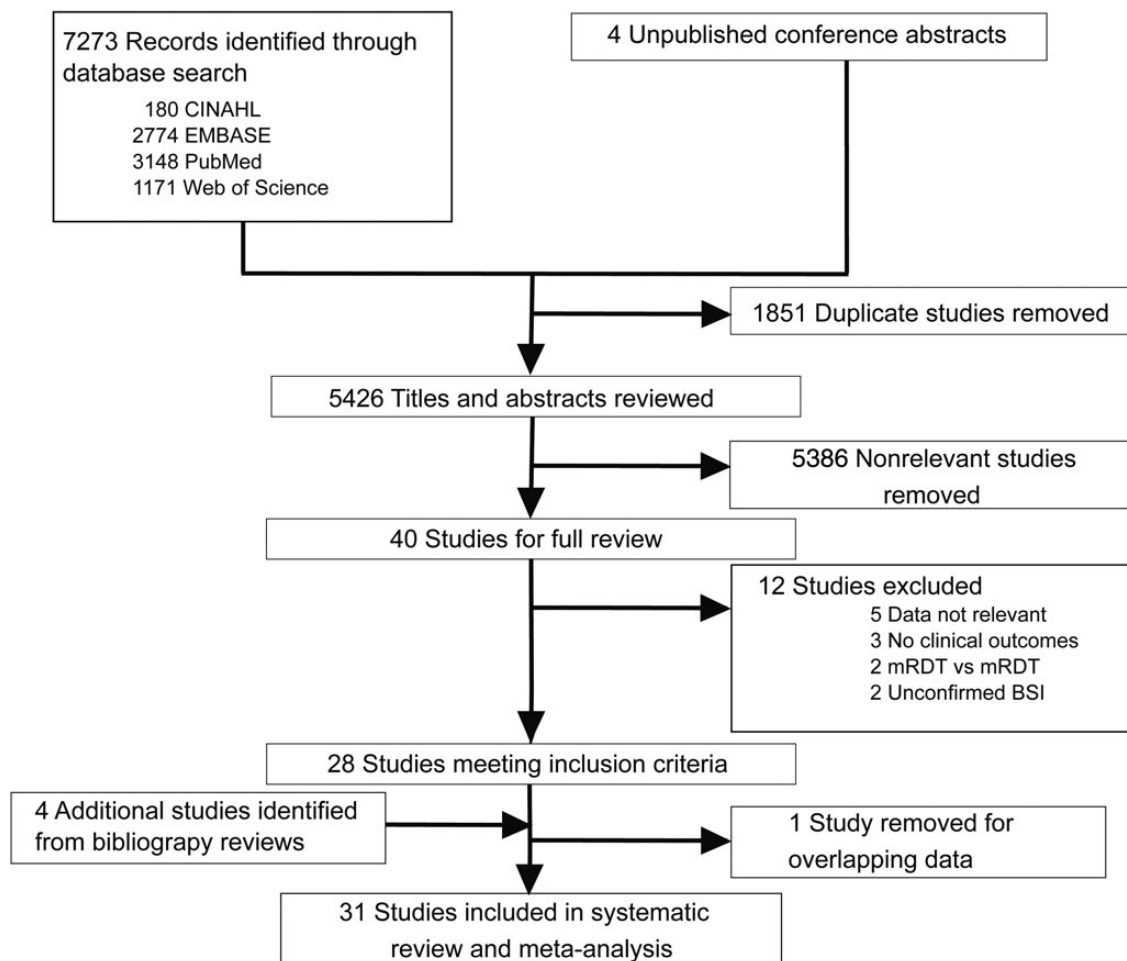
**Figure 1.** Flow diagram. Abbreviations: BSI, bloodstream infection; mRDT, molecular rapid diagnostic testing.

17 studies (54.8%), followed by gram-negative organisms with 7 studies (22.6%). Multiple organism and yeast studies comprised the remainder, with 5 (16.1%) and 2 (6.5%) of the studies, respectively.

Laboratory practices varied among studies, including mRDT technologies used, frequency of testing, and reporting processes. PCR or other microarray technologies were most frequently used (20 of 31 studies; 64.5%), followed by PNA-FISH (6 of 31; 19.4%) and MALDI-TOF analysis (4 of 31; 12.9%). One study (3.2%) used both a nanotechnology microarray system and confirmatory MALDI-TOF analysis [41]. A distinction between MALDI-TOF analysis of direct blood specimens and overnight solid media incubation was reported in 4 of 5 MALDI-TOF studies [15, 29, 30, 36], with a single study [29] reporting the latter method. Of the 19 studies reporting the frequency of laboratory sample testing, 5 (26.3%) reported real-time testing, 10 (52.6%) reported batch testing between 1 to 4 times daily, and 3 (15.8%) reported real-time testing during limited time frames (eg, 7 AM to 7 PM). Among the 5 studies performing real-time testing 24 hours a day, 7 days a week (24 × 7),

mRDT result notifications were reported as being performed in real time for 2 studies [17, 33], whereas in another study [45] the protocol called for real-time notification only if resistance genes were detected. Finally, notification methods also varied between studies when reported, with the majority of the reporting studies (17 of 29; 58.6%) reporting directly to the primary team or physician and 3 studies (10.3%) reporting to the results to nurses.

ASP activities varied by study. The presence of an ASP facilitating mRDT represented the majority of the data (20 of 31 studies; 64.5%). In the 14 studies reporting ASP notification processes, only half were 24 × 7 real-time. The remainder had set response hours (eg, 8 AM to 5 PM; Monday–Friday) or once daily review of results. Two studies [17, 20], both quasi-experimental, explicitly stated whether the ASP was present in both periods, with 1 [20] having an ASP in the postintervention period only.

Clinical outcomes in BSIs generally favored mRDT over conventional microbiology (Figures 2 and 3). Among 26 studies [5, 15, 18–20, 22–27, 29–34, 36, 37, 39, 40, 42–46], the ORs for mortality risk were significantly lower with mRDT (OR, 0.66; 95% CI, .54–.80), yielding a number needed to treat of 20.

**Table 1. Characteristics of Studies Included in Systematic Review and Meta-analysis**

| Authors (Year) | Study Design | Setting | Patient Population | Sample Size, mRDT/ Control, No. of Patients | BSI Type | Laboratory Tests | mRDT Testing; Notification Recipient | ASP Presence | ASP Notification Process | NOS Score |
|---|---|---|---|---|---|---|---|---|---|---|
| Bauer et al [17] (2010) | Quasi-experimental | Tertiary care facility (1150 beds) | Adult | 82/74 | *Staphylococcus aureus* | Conventional vs PCR | 24 × 7; physician | Yes | Real-time (M–F; 8 AM–5 PM) | 9 |
| Beuving et al [18] (2015) | RCT | Hospital (750 beds) | Adult | 129/121 | Multiple | Conventional vs PCR | NR; physician | No | NA | NA |
| Bias et al [19] (2015) | Quasi-experimental | NR | Adult | 49/65 | Gram-negative organisms | Conventional vs BC-GN | NR; physician and ASP | Yes | NR | 7 |
| Box et al [20] (2015) | Quasi-experimental | 5 Community hospitals | Adult | 64/103 | Gram-positive organisms | Conventional vs BC-GP | 7 AM–7 AM; nurse | Yes | Real-time (7 AM–7 PM) | 7 |
| Cattoir et al [21] (2011) | Quasi-experimental | Teaching hospital (900 beds) | Adult | 49/48 | *Staphylococcus* spp. | Conventional vs PCR | NR; physician | No | NA | 9 |
| Felsenstein et al [22] (2016) | Quasi-experimental | Children's hospital | Pediatric | 219/221 | Gram-positive organisms | Conventional vs BC-GP | 24 × 7 testing but not real time; physician | No | NA | 8 |
| Forrest et al [23] (2006) | Quasi-experimental | Medical center | NR | 72/76 | Yeast | Conventional vs PNA-FISH | Once daily; team and ASP | Yes | Real-time | 7 |
| Forrest et al [24] (2006) | Case-control | Medical center (740 beds) | NR | 119/84 | CoNS | Conventional vs PNA-FISH | Once daily; team and ASP | Yes | Real-time | 9 |
| Forrest et al [25] (2008) | Quasi-experimental | Teaching hospital (600 beds) | Adult | 95/129 | *Enterococcus* spp. | Conventional vs PNA-FISH | Twice daily; physician and ASP | Yes | Real-time | 7 |
| Frye et al [26] (2012) | Quasi-experimental | 2 Medical centers (each 500 beds) | Adult | 110/134 | *Staphylococcus* spp. | Conventional vs PCR | Twice daily M–F, once daily Sat–Sun; MRSA results to floor | No | NA | 9 |
| Heil et al [27] (2012) | Quasi-experimental | NR | Adult | 21/61 | Yeast | Conventional vs PNA-FISH | 7 AM–9:30 PM; physician and pharmacist | Yes | Real-time | 7 |
| Holtzman et al [28] (2011) | Quasi-experimental | Medical center | Adult | 99/100 | CoNS | Conventional vs PNA-FISH | Once daily; EHR only | No | NA | 9 |
| Huang et al [29] (2013) | Quasi-experimental | Health system | Adult | 245/256 | Multiple | Conventional vs MALDI-TOF | NR; ordering clinician and ASP | Yes | 6 AM–11:30 PM | 9 |
| Lockwood et al [30] (2016) | Quasi-experimental | 2 Community hospitals | Adult | 241/149 | Gram-negative organisms | Conventional vs MALDI-TOF | NR; nurse and ASP | Yes | Real-time | 7 |
| Ly et al [31] (2008) | RCT | Tertiary care center (907 beds) | Adult | 101/101 | *Staphylococcus* spp. | Conventional vs PNA-FISH | Twice daily; treating clinician | No | NA | NA |
| Macvane et al [32] (2015) | Quasi-experimental | NR | Adult | 63/50 | Gram-negative organisms | Conventional vs PCR | NR; NR | Yes | NR | 7 |
| Macvane et al [33] (2016) | Quasi-experimental | Academic center (709 beds) | Adult | 23/45 | *Enterococcus* spp. | Conventional vs PCR | 24 × 7; nurse and pharmacist | Yes | Real-time (8 AM–5 PM; M–F) | 7 |
| Maslonka et al [34] (2014) | Case-Control | NR | NR | 55/55 | Multiple | Conventional vs PCR | NR; NR | No | NA | 7 |
| Na et al [35] (2016) | Quasi-experimental | Academic hospital | NR | 97/94 | *Staphylococcus* spp. | Conventional vs PCR | Once daily M–Sat; EHR only | No | NA | 7 |
| Nagel et al [36] (2014) | Quasi-experimental | Health system | Adult | 117/129 | CoNS | Conventional vs MALDI-TOF | NR; physician and ASP | Yes | 6 AM–11:30 AM | 7 |
| Neuberger et al [37] (2008) | Quasi-experimental | Tertiary care medical center | NR | 42/42 | *Klebsiella pneumoniae* | Conventional vs PCR | 11 PM–11 AM M–F; physician | No | NA | 9 |
| Nguyen et al [38] (2010) | Quasi-experimental | Academic hospital | Adult | 94/65 | *Staphylococcus* spp. | Conventional vs PCR | NR; EHR only | No | NA | 9 |
| Pardo et al [39] (2016) | Case-control | Academic medical center (939 beds) | Adult | 84/252 | Multiple | Conventional vs PCR | Once daily; ASP | Yes | NR | 9 |
| Perez et al [15] (2013) | Quasi-experimental | Quaternary care academic hospital (1000 beds) | Adult | 107/112 | Gram-negative organisms | Conventional vs MALDI-TOF | 3–4 times daily; ASP | Yes | Real-time | 9 |
| Revolinksi et al [40] (2015) | Quasi-experimental | NR | Adult | 95/133 | Gram-positive organisms | Conventional vs BC-GP | NR; provider and pharmacist | Yes | NR | 7 |
| Roshdy et al [41] (2015) | Quasi-experimental | Academic medical center | NR | 74/65 | *Streptococcus/ Enterococcus* spp. | Conventional vs BC-GP plus MALDI-TOF | NR; pharmacist | Yes | NR | 7 |

Table 1 continued.

| Authors (Year) | Study Design | Setting | Patient Population | Sample Size, mRDT/Control, No. of Patients | BSI Type | Laboratory Tests | mRDT Testing; Notification Recipient | ASP Presence | ASP Notification Process | NOS Score |
|---|---|---|---|---|---|---|---|---|---|---|
| Sango et al [42] (2013) | Quasi-experimental | Academic medical center (695 beds) | NR | 28/46 | *Enterococcus* spp. | Conventional vs BC-GP | 24 × 7; ASP | Yes | M–F; 7:30 AM–5 PM | 7 |
| Sothoron et al [43] (2015) | Quasi-experimental | NR | Adult | 67/59 | Gram-negative organisms | Conventional vs BC-GN | 24 × 7; ASP | Yes | Real-time | 7 |
| Suzuki et al [44] (2015) | Quasi-experimental | Tertiary medical center (413 beds) | NR | 88/147 | Multiple | Conventional vs BC-GP/GN | NR; hospital physician and infectious diseases physician | Yes | NR | 7 |
| Walker et al [45] (2016) | Quasi-experimental | Tertiary care hospital (401 beds) and cancer hospital (60 beds) | NR | 97/98 | Gram-negative organisms | Conventional vs BC-GN | 24 × 7; physician if resistant organism | Yes | Daily | 9 |
| Wang et al [46] (2013) | Quasi-experimental | Tertiary care hospital (1200 beds) | NR | 48/38 | *Staphylococcus* spp. | Conventional vs PCR | Once daily; physician | No | NA | 7 |

Abbreviations: 24 × 7, 24 hours a day, 7 days a week; ASP, antimicrobial stewardship program; BC-GN, blood culture gram-negative nanotechnology microarray system; BC-GP, blood culture gram-positive nanotechnology microarray system; BSI, bloodstream infection; CoNS, coagulase-negative *Staphylococcus* species; EHR, electronic health record; M–F, Monday–Friday; M–Sat, Monday–Saturday; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight analysis; mRDT, molecular rapid diagnostic testing; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; NOS, Newcastle-Ottawa Scale; NR, not reported; PCR, polymerase chain reaction; PNA-FISH, peptide nucleic acid fluorescent in situ hybridization; RCT, randomized controlled trial; Sat–Sun, Saturday and Sunday.

Stratification revealed that the ORs for mortality risk were significantly lower for BSIs using mRDT with ASP (OR, 0.64; 95% CI, .51–.79) but failed to achieve significance without ASP support (0.72; 95% CI, .46–1.12). Similar results were observed when a sensitivity analysis was performed using studies that controlled for confounding [18, 24, 29, 31, 37, 39, 45] (Supplementary Figure 1). When mortality risk was evaluated by organism type (Figure 3), there was no significant difference in the odds of mortality among yeast isolates (OR, 0.90; 95% CI, .49–1.67). In contrast, the odds of mortality were reduced with mRDT in studies of gram-negative (OR, 0.51; 95% CI, .33–.78), gram-positive (0.73; .55–.97), and multiple organism types (0.58; .32–1.04). Mortality risk in testing of multiple organisms had significant heterogeneity (Cochran's $Q$ $P = .07$; $I^2 = 53\%$) owing to a study [18] that used both mRDT and rapid susceptibility testing. Exclusion of that study yielded a 51% decreased odds of mortality in multiple organism testing (OR, 0.49; 95% CI, .33–.71; Cochran's $Q$ $P = .56$; $I^2 = 0\%$). Sensitivity analysis using studies controlling for confounding [18, 24, 29, 31, 37, 39, 45] achieved nonsignificant reductions in mortality risk for each organism group (Supplementary Figure 2). Meta-regressions of covariates by the presence of an ASP ($P = .56$), organism type ($P = .42$), real-time ASP ($P = .82$), or real-time mRDT ($P = .34$) as possible moderators for mortality risk were not significant.

Among 9 studies [21, 29, 32–35, 37, 40, 41], time to effective therapy (Supplementary Figure 3) was significantly decreased by a weighted mean difference of −5.03 hours (95% CI, −8.60 to −1.45 hours) for mRDT versus conventional microbiology. Time to effective therapy had significant heterogeneity (Cochran's $Q$ $P = .0002$; $I^2 = 74\%$) owing to a study [33] that was limited to vancomycin-resistant enterococci (VRE). Exclusion of that study yielded a time to effective therapy with a decreased weighted mean difference of −1.89 hours (95% CI, −2.43 to −1.36 hours; Cochran's $Q$ $P = .48$; $I^2 = 0\%$). Evaluation of that study [33] and VRE subgroup data from 2 studies [39, 41] yielded a time to effective therapy weighted mean difference of −26.65 hours (95% CI, −35.43 to −17.88 hours; Cochran's $Q$ $P = .66$; $I^2 = 0\%$). Finally, LOS (Supplementary Figure 4) was significantly shorter with mRDT, by −2.48 days (95% CI, −3.90 to −1.06 days) and similar results were observed among subgroups by total hospital LOS and from culture LOS. Sensitivity analysis was performed using the only 2 studies [18, 39] that controlled for confounding and reflected a decreased LOS by a WMD of −8.08 days (95% CI, −20.59 to 4.44 days; Cochran's $Q$ $P < .0001$; $I^2 = 95\%$).

Analysis of the potential for publication bias with funnel plots (Supplementary Figures 5–7) suggested no evidence of publication bias for the analyses presented in Figures 2 and 3 and Supplementary Figure 3. Similarly, Egger's regression testing reflected an absence of publication bias for the analyses presented in Figures 2 and 3 and Supplementary Figure 3 ($P = .98$,
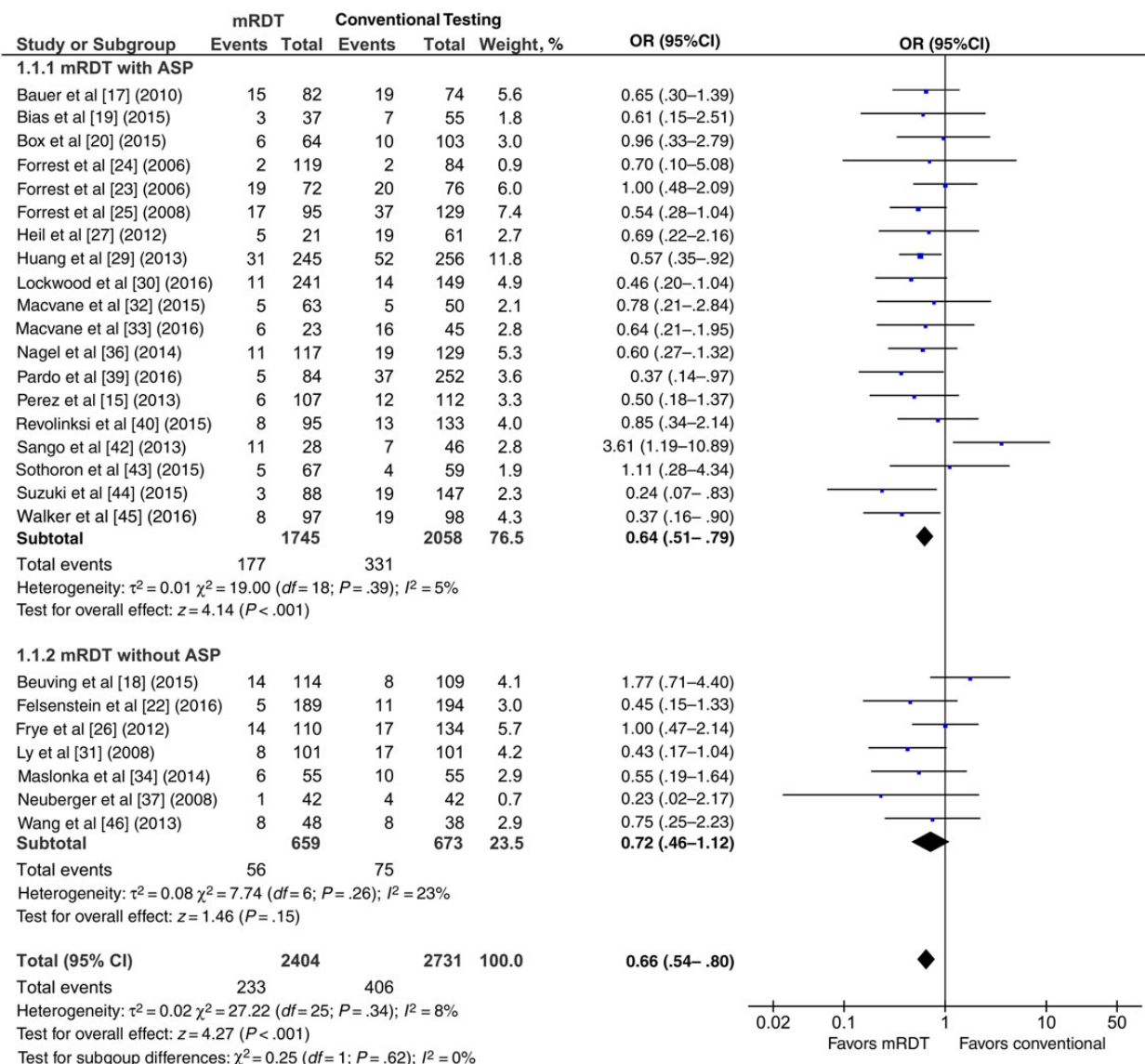
| Study or Subgroup | mRDT Events | Total | Conventional Testing Events | Total | Weight, % | OR (95%CI) |
|---|---|---|---|---|---|---|
| **1.1.1 mRDT with ASP** | | | | | | |
| Bauer et al [17] (2010) | 15 | 82 | 19 | 74 | 5.6 | 0.65 (.30–1.39) |
| Bias et al [19] (2015) | 3 | 37 | 7 | 55 | 1.8 | 0.61 (.15–2.51) |
| Box et al [20] (2015) | 6 | 64 | 10 | 103 | 3.0 | 0.96 (.33–2.79) |
| Forrest et al [24] (2006) | 2 | 119 | 2 | 84 | 0.9 | 0.70 (.10–5.08) |
| Forrest et al [23] (2006) | 19 | 72 | 20 | 76 | 6.0 | 1.00 (.48–2.09) |
| Forrest et al [25] (2008) | 17 | 95 | 37 | 129 | 7.4 | 0.54 (.28–1.04) |
| Heil et al [27] (2012) | 5 | 21 | 19 | 61 | 2.7 | 0.69 (.22–2.16) |
| Huang et al [29] (2013) | 31 | 245 | 52 | 256 | 11.8 | 0.57 (.35–.92) |
| Lockwood et al [30] (2016) | 11 | 241 | 14 | 149 | 4.9 | 0.46 (.20–1.04) |
| Macvane et al [32] (2015) | 5 | 63 | 5 | 50 | 2.1 | 0.78 (.21–.2.84) |
| Macvane et al [33] (2016) | 6 | 23 | 16 | 45 | 2.8 | 0.64 (.21–.1.95) |
| Nagel et al [36] (2014) | 11 | 117 | 19 | 129 | 5.3 | 0.60 (.27–1.32) |
| Pardo et al [39] (2016) | 5 | 84 | 37 | 252 | 3.6 | 0.37 (.14–.97) |
| Perez et al [15] (2013) | 6 | 107 | 12 | 112 | 3.3 | 0.50 (.18–1.37) |
| Revolinksi et al [40] (2015) | 8 | 95 | 13 | 133 | 4.0 | 0.85 (.34–2.14) |
| Sango et al [42] (2013) | 11 | 28 | 7 | 46 | 2.8 | 3.61 (1.19–10.89) |
| Sothoron et al [43] (2015) | 5 | 67 | 4 | 59 | 1.9 | 1.11 (.28–4.34) |
| Suzuki et al [44] (2015) | 3 | 88 | 19 | 147 | 2.3 | 0.24 (.07– .83) |
| Walker et al [45] (2016) | 8 | 97 | 19 | 98 | 4.3 | 0.37 (.16– .90) |
| **Subtotal** | | **1745** | | **2058** | **76.5** | **0.64 (.51– .79)** |
| Total events | 177 | | 331 | | | |

Heterogeneity: $\tau^2 = 0.01$ $\chi^2 = 19.00$ ($df = 18$; $P = .39$); $I^2 = 5\%$
Test for overall effect: $z = 4.14$ ($P < .001$)

| | mRDT Events | Total | Conventional Testing Events | Total | Weight, % | OR (95%CI) |
|---|---|---|---|---|---|---|
| **1.1.2 mRDT without ASP** | | | | | | |
| Beuving et al [18] (2015) | 14 | 114 | 8 | 109 | 4.1 | 1.77 (.71–4.40) |
| Felsenstein et al [22] (2016) | 5 | 189 | 11 | 194 | 3.0 | 0.45 (.15–1.33) |
| Frye et al [26] (2012) | 14 | 110 | 17 | 134 | 5.7 | 1.00 (.47–2.14) |
| Ly et al [31] (2008) | 8 | 101 | 17 | 101 | 4.2 | 0.43 (.17–1.04) |
| Maslonka et al [34] (2014) | 6 | 55 | 10 | 55 | 2.9 | 0.55 (.19–1.64) |
| Neuberger et al [37] (2008) | 1 | 42 | 4 | 42 | 0.7 | 0.23 (.02–2.17) |
| Wang et al [46] (2013) | 8 | 48 | 8 | 38 | 2.9 | 0.75 (.25–2.23) |
| **Subtotal** | | **659** | | **673** | **23.5** | **0.72 (.46–1.12)** |
| Total events | 56 | | 75 | | | |

Heterogeneity: $\tau^2 = 0.08$ $\chi^2 = 7.74$ ($df = 6$; $P = .26$); $I^2 = 23\%$
Test for overall effect: $z = 1.46$ ($P = .15$)

| | | Total | | Total | Weight, % | OR (95%CI) |
|---|---|---|---|---|---|---|
| **Total (95% CI)** | | **2404** | | **2731** | **100.0** | **0.66 (.54– .80)** |
| Total events | 233 | | 406 | | | |

Heterogeneity: $\tau^2 = 0.02$ $\chi^2 = 27.22$ ($df = 25$; $P = .34$); $I^2 = 8\%$
Test for overall effect: $z = 4.27$ ($P < .001$)
Test for subgroup differences: $\chi^2 = 0.25$ ($df = 1$; $P = .62$); $I^2 = 0\%$

**Figure 2.** Mortality outcomes with molecular rapid diagnostic testing (mRDT) versus conventional testing in bloodstream infection. Odds ratios (ORs) were determined with the Mantel-Haenszel random-effects method. Abbreviations: ASP, antimicrobial stewardship program; CI, confidence interval.

$P = .98$, and $P = .07$, respectively). However, results of Egger's regression testing suggested possible publication bias with the LOS analysis (Supplementary Figure 4; $P = .01$).

## DISCUSSION

In this systematic review and meta-analysis of 31 studies and 5920 BSI patients, mRDT was associated with a decreased mortality risk and LOS, as well as improved time to effective therapy, compared with conventional microbiologic methods. The extent of adoption of mRDT for BSIs among acute care facilities in the United States is unknown, although the National Action Plan for Combating Antibiotic-Resistant Bacteria [6] has called for the use of RDT to identify drug-resistant organisms and improve stewardship. Although a number of observational studies

have supported the use of mRDT with ASPs for improving clinical outcomes, results of a randomized control trial [47] suggest that these technologies have a limited impact [47]. However, this study's definition of standard blood culture processing included MALDI-TOF analysis, so mRDT was included in both comparator groups.

Clinical implications for the use of RDT in BSIs have been evaluated in 1 meta-analysis [9]. Although that meta-analysis evaluated the use of RDT with communication of results to providers, it did not explore the role of ASP. It was also limited by the time frame of its literature review, and it did not focus solely on molecular technologies. In our current meta-analysis with 16 additional studies, we specifically explored the relationship between mRDT and ASP. We found that mortality risk decreased
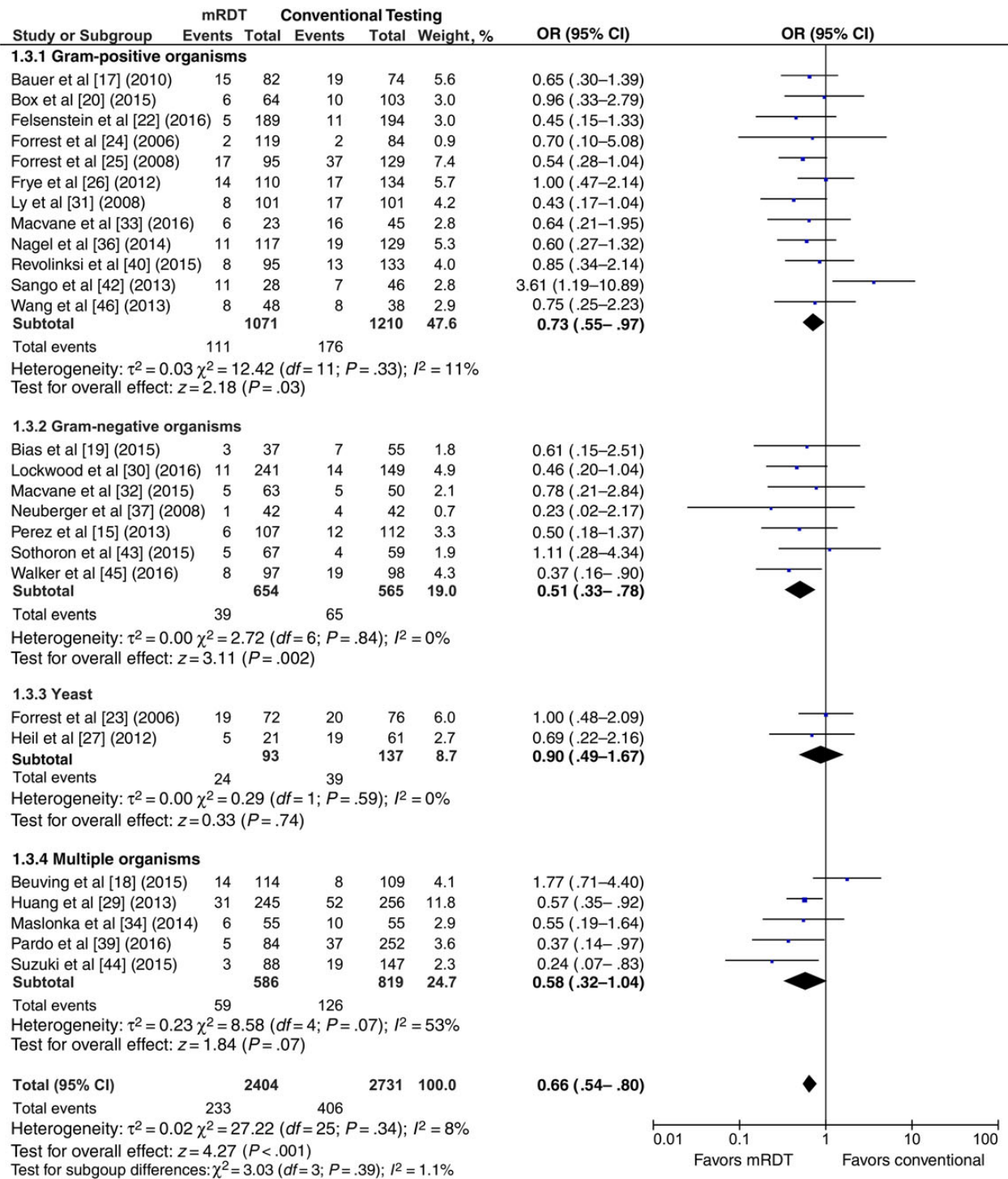
|  | mRDT | | Conventional Testing | | | | |
|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight, % | OR (95% CI) | OR (95% CI) |
| **1.3.1 Gram-positive organisms** | | | | | | | |
| Bauer et al [17] (2010) | 15 | 82 | 19 | 74 | 5.6 | 0.65 (.30–1.39) | |
| Box et al [20] (2015) | 6 | 64 | 10 | 103 | 3.0 | 0.96 (.33–2.79) | |
| Felsenstein et al [22] (2016) | 5 | 189 | 11 | 194 | 3.0 | 0.45 (.15–1.33) | |
| Forrest et al [24] (2006) | 2 | 119 | 2 | 84 | 0.9 | 0.70 (.10–5.08) | |
| Forrest et al [25] (2008) | 17 | 95 | 37 | 129 | 7.4 | 0.54 (.28–1.04) | |
| Frye et al [26] (2012) | 14 | 110 | 17 | 134 | 5.7 | 1.00 (.47–2.14) | |
| Ly et al [31] (2008) | 8 | 101 | 17 | 101 | 4.2 | 0.43 (.17–1.04) | |
| Macvane et al [33] (2016) | 6 | 23 | 16 | 45 | 2.8 | 0.64 (.21–1.95) | |
| Nagel et al [36] (2014) | 11 | 117 | 19 | 129 | 5.3 | 0.60 (.27–1.32) | |
| Revolinksi et al [40] (2015) | 8 | 95 | 13 | 133 | 4.0 | 0.85 (.34–2.14) | |
| Sango et al [42] (2013) | 11 | 28 | 7 | 46 | 2.8 | 3.61 (1.19–10.89) | |
| Wang et al [46] (2013) | 8 | 48 | 8 | 38 | 2.9 | 0.75 (.25–2.23) | |
| Subtotal | | 1071 | | 1210 | 47.6 | **0.73 (.55–.97)** | |
| Total events | 111 | | 176 | | | | |

Heterogeneity: $\tau^2 = 0.03$ $\chi^2 = 12.42$ ($df = 11$; $P = .33$); $I^2 = 11\%$
Test for overall effect: $z = 2.18$ ($P = .03$)

| **1.3.2 Gram-negative organisms** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Bias et al [19] (2015) | 3 | 37 | 7 | 55 | 1.8 | 0.61 (.15–2.51) | |
| Lockwood et al [30] (2016) | 11 | 241 | 14 | 149 | 4.9 | 0.46 (.20–1.04) | |
| Macvane et al [32] (2015) | 5 | 63 | 5 | 50 | 2.1 | 0.78 (.21–2.84) | |
| Neuberger et al [37] (2008) | 1 | 42 | 4 | 42 | 0.7 | 0.23 (.02–2.17) | |
| Perez et al [15] (2013) | 6 | 107 | 12 | 112 | 3.3 | 0.50 (.18–1.37) | |
| Sothoron et al [43] (2015) | 5 | 67 | 4 | 59 | 1.9 | 1.11 (.28–4.34) | |
| Walker et al [45] (2016) | 8 | 97 | 19 | 98 | 4.3 | 0.37 (.16–.90) | |
| Subtotal | | 654 | | 565 | 19.0 | **0.51 (.33–.78)** | |
| Total events | 39 | | 65 | | | | |

Heterogeneity: $\tau^2 = 0.00$ $\chi^2 = 2.72$ ($df = 6$; $P = .84$); $I^2 = 0\%$
Test for overall effect: $z = 3.11$ ($P = .002$)

| **1.3.3 Yeast** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Forrest et al [23] (2006) | 19 | 72 | 20 | 76 | 6.0 | 1.00 (.48–2.09) | |
| Heil et al [27] (2012) | 5 | 21 | 19 | 61 | 2.7 | 0.69 (.22–2.16) | |
| Subtotal | | 93 | | 137 | 8.7 | **0.90 (.49–1.67)** | |
| Total events | 24 | | 39 | | | | |

Heterogeneity: $\tau^2 = 0.00$ $\chi^2 = 0.29$ ($df = 1$; $P = .59$); $I^2 = 0\%$
Test for overall effect: $z = 0.33$ ($P = .74$)

| **1.3.4 Multiple organisms** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Beuving et al [18] (2015) | 14 | 114 | 8 | 109 | 4.1 | 1.77 (.71–4.40) | |
| Huang et al [29] (2013) | 31 | 245 | 52 | 256 | 11.8 | 0.57 (.35–.92) | |
| Maslonka et al [34] (2014) | 6 | 55 | 10 | 55 | 2.9 | 0.55 (.19–1.64) | |
| Pardo et al [39] (2016) | 5 | 84 | 37 | 252 | 3.6 | 0.37 (.14–.97) | |
| Suzuki et al [44] (2015) | 3 | 88 | 19 | 147 | 2.3 | 0.24 (.07–.83) | |
| Subtotal | | 586 | | 819 | 24.7 | **0.58 (.32–1.04)** | |
| Total events | 59 | | 126 | | | | |

Heterogeneity: $\tau^2 = 0.23$ $\chi^2 = 8.58$ ($df = 4$; $P = .07$); $I^2 = 53\%$
Test for overall effect: $z = 1.84$ ($P = .07$)

| **Total (95% CI)** | | 2404 | | 2731 | 100.0 | **0.66 (.54–.80)** | |
|---|---|---|---|---|---|---|---|
| Total events | 233 | | 406 | | | | |

Heterogeneity: $\tau^2 = 0.02$ $\chi^2 = 27.22$ ($df = 25$; $P = .34$); $I^2 = 8\%$
Test for overall effect: $z = 4.27$ ($P < .001$)
Test for subgoup differences: $\chi^2 = 3.03$ ($df = 3$; $P = .39$); $I^2 = 1.1\%$

0.01  0.1  1  10  100
Favors mRDT    Favors conventional

**Figure 3.** Mortality with molecular rapid diagnostic testing (mRDT) versus conventional testing by organism type in bloodstream infection. Odds ratios (ORs) were determined with the Mantel-Haenszel random-effects method. Abbreviation: CI, confidence interval.

significantly with mRDT in the presence of ASP but not in its absence. Thus, we believe our results support the Infectious Diseases Society of America ASP guideline recommendation to use RDT with ASP facilitation in BSIs [7]. Moreover, our analysis indicates that mRDT would only need to be used in approximately 20 patients with BSI to prevent 1 death within 30 days, which further supports mRDT as the standard of care in BSIs.

Compared with conventional microbiologic methods, mRDT was associated with significantly decreased mortality risk among studies including gram-negative organisms, gram-positive

organisms, and multiple infection types, whereas yeast studies did not achieve significant mortality reductions. However, among studies controlling for confounding [18, 24, 29, 31, 37, 39, 45], nonsignificant reductions in mortality risk were observed by organism groups. Failure to demonstrate the benefit of mRDT for mortality risk associated with yeast BSIs or among studies in the sensitivity analysis may reflect the limited number of studies and corresponding sample sizes.

Detecting true mortality benefits may be difficult in pre- and postintervention studies that have not controlled for confounding. Therefore, the use of an outcome more directly related to mRDT, such as time to effective therapy, may be a better indicator of mRDT benefits. Although few studies reported time to effective therapy, we did observe a significant decrease in this parameter. However, the distribution of time to effective therapy varied both within and between studies. The importance of this measure was demonstrated in a study of VRE bacteremia [3], whose authors reported a 3-fold increase in 30-day mortality in the absence of effective therapy in the first 48 hours of BSI and speculated that RDT may help reduce the time to effective therapy in the setting of VRE. Our results suggest the particular utility of mRDT in VRE BSIs, improving time to effective therapy by >24 hours. Furthermore, the mean time to effective therapy for all 3 VRE studies included in our analysis ranged from 43.7 to 50.2 hours. We therefore believe that mRDT may have profound benefits in patients with VRE bacteremia and may help minimize mortality risk in this population.

Finally, we observed significant decreases in LOS. Although we did not evaluate costs, the observed decreases in LOS have significant implications based on cost savings per day of hospitalization avoided. A study evaluating the economic impact of mRDT in BSI demonstrated an estimated $30 000 cost savings per 100 patients after accounting for mRDT costs [39]. However, the generalizability of decreased LOS reported are probably limited to large hospitals and medical centers, because only 2 of the included studies were conducted in community hospitals. In addition, LOS did not achieve significant reductions in the 2 studies that controlled for confounding [18, 39], although the significant heterogeneity in this analysis and small sample limit inference of these results.

Our systematic review and meta-analysis have several limitations. For LOS, our analysis suggested possible publication bias. However, this may be related to the small number of studies reporting this outcome. Although the generalizability of our findings for clinical outcomes may be limited to academic medical centers, it should be noted that 2 community hospital studies were included [20, 30]. In 1 of these studies, although an ASP was present, pharmacists not trained in infectious diseases responded to the BSIs [30]. Future studies from the community hospital setting elucidating outcomes would help clarify best practices in this area. Guidance for recording and reporting these outcomes when using RDT in BSIs has been described

and should be used by researchers in the future [9]. In addition, we treated all interventions as equal with regard to technology type, owing to variability in laboratory practices, such as batching of assays or performance of MALDI-TOF analysis, either directly from blood culture bottles containing nutritional broth or from solid agar incubated overnight. Notification methods for mRDT results also varied, which could have implications for clinical outcomes. Although future evaluations may consider these variations and their relationship to clinical outcomes, our analysis supports mRDT as a group improves outcomes in BSIs. In addition, we believe the implementation of mRDT should include an action plan to ensure correct interpretation, real-time reporting, and guidance on optimal therapy. Having 24 × 7 testing, with immediate notifications to the provider along with direction from an ASP team, will facilitate the initiation, escalation, or de-escalation of therapy in a meaningful time frame.

In conclusion, mRDT was associated with significant decreases in mortality risk in the presence of an ASP, but not in its absence. Significant decreases in mortality risk were also seen for studies including gram-positive organisms, gram-negative organisms, and multiple organism types. In addition, mRDT was associated with decreased time to effective therapy and LOS. The greatest benefit of mRDT for improving time to effective therapy may be for BSIs caused by resistant organisms, particularly VRE. Additional studies in community hospitals are needed, as are additional studies elucidating the benefits of various microbiologic technologies in combination with ASP to define best practices. Based on the clinical outcomes, mRDT should be considered as part of the standard of care in patients with BSIs.

## Supplementary Data

## Notes

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