

Effectiveness of Practices To Increase Timeliness of Providing Targeted Therapy for Inpatients with Bloodstream Infections: a Laboratory Medicine Best Practices Systematic Review and Meta-analysis

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SUMMARY

Background. Bloodstream infection (BSI) is a major cause of morbidity and mortality throughout the world. Rapid identification of bloodstream pathogens is a laboratory practice that supports strategies for rapid transition to direct targeted therapy by providing for timely and effective patient care. In fact, the more rapidly that appropriate antimicrobials are prescribed, the lower the mortality for patients with sepsis. Rapid identification methods may have multiple positive impacts on patient outcomes, including reductions in mortality, morbidity, hospital lengths of stay, and antibiotic use. In addition, the strategy can reduce the cost of care for patients with BSIs.

Objectives. The purpose of this review is to evaluate the evidence for the effectiveness of three rapid diagnostic practices in decreasing the time to targeted therapy for hospitalized patients with BSIs. The review was performed by applying the Centers for Disease Control and Prevention's (CDC's) Laboratory Medicine Best Practices Initiative (LMBP) systematic review methods for quality improvement (QI) practices and translating the results into evidence-based guidance (R. H. Christenson et al., *Clin Chem* 57:816–825, 2011, <http://dx.doi.org/10.1373/clinchem.2010.157131>).

Search strategy. A comprehensive literature search was conducted to identify studies with measurable outcomes. A search of three electronic bibliographic databases (PubMed, Embase, and CINAHL), databases containing “gray” literature (unpublished academic, government, or industry evidence not governed by commercial publishing) (CIHI, NIHR, SIGN, and other databases), and the Cochrane database for English-language articles published between 1990 and 2011 was conducted in July 2011.

Dates of search. The dates of our search were from 1990 to July 2011.

Selection criteria. Animal studies and non-English publications were excluded. The search contained the following medical subject headings: bacteremia; bloodstream infection; time factors; health care costs; length of stay; morbidity; mortality; antimicrobial therapy; rapid molecular techniques, polymerase chain reaction (PCR); *in situ* hybridization, fluorescence; treatment outcome; drug therapy; patient care team; pharmacy service, hospital; hospital information systems; Gram stain; pharmacy service; and spectrometry, mass, matrix-assisted laser desorption-ionization.

Phenotypic as well as the following key words were searched: targeted therapy; rapid identification; rapid; Gram positive; Gram negative; reduce(ed); cost(s); pneumoslide; PBP2; tube coagulase; matrix-assisted laser desorption/ionization time of flight; MALDI TOF; blood culture; EMR; electronic reporting; call to provider; collaboration; pharmacy; laboratory; bacteria; yeast; ICU; and others. In addition to the electronic search being performed, a request for unpublished quality improvement data was made to the clinical laboratory community.

Main results. Rapid molecular testing with direct communication significantly improves timeliness compared to standard testing. Rapid phenotypic techniques with direct communication likely improve the timeliness of targeted therapy. Studies show a significant and homogeneous reduction in mortality associated with rapid molecular testing combined with direct communication.

Authors' conclusions. No recommendation is made for or against the use of the three assessed practices of this review due to insufficient evidence. The overall strength of evidence is suggestive; the data suggest that each of these three practices has the potential to improve the time required to initiate targeted therapy and possibly improve other patient outcomes, such as mortality. The meta-analysis results suggest that the implementation of any of the three practices may be more effective at increasing timeliness to targeted therapy than routine microbiology techniques for identification of the microorganisms causing BSIs. Based on the included studies, results for all three practices appear applicable across multiple microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), *Candida* species, and *Enterococcus* species.

INTRODUCTION

Bloodstream infection (BSI) is a major cause of morbidity and mortality throughout the world (2–5). In 2002, over 30,000 deaths in U.S. hospitals were due to BSIs, and the incidence continues to increase (6). During the period from 2000 to 2010, mortality from septicemia grew by 17% (7), and recent reports still show mortality to range from 34 to 52% (8). In 2009, septicemia, a severe BSI caused by bacteria in the blood, affected nearly 1 out of every 23 hospitalized patients (4.2%) and was the sixth most common reason for hospitalization in the United States (9).

Microorganisms enter the bloodstream through various por-

tals, including dissemination from a previous or concomitant infection and access via surgical sites, intravenous catheters, and other vascular access devices (10). Bloodstream infections can be caused by a wide variety of microorganisms, commonly *Escherichia coli*, *Klebsiella* spp., *Staphylococcus aureus*, *Enterococcus* spp., other bacteria, and yeast. These infections can lead to increased mortality, long-term disability, excess length of stay (LOS) in hospitals, large additional costs for health systems, and high costs as well as loss of quality of life for patients and their families. For example, septicemia was the single most expensive condition at U.S. hospitals in 2009, with an aggregate cost of \$15.4 billion (9) or 4.3% of all hospital costs. The effect of nosocomial bloodstream infections indicates that health care-associated BSIs result in an additional LOS of over 10 days (11).

Rapid identification of bloodstream pathogens is a laboratory practice that supports rapid transitions to direct targeted therapy, leveraging results to support timely and effective patient care. In fact, the more rapidly appropriate antimicrobials are prescribed, the lower the mortality for patients with sepsis (12–14). Rapid identification methods may have multiple positive impacts on patient outcomes, including reductions in mortality, morbidity, hospital LOS, antibiotic use, and health care expenses (15–17).

QUALITY GAP: DELAYS IN IDENTIFICATION OF BSIs

Traditional identification and antimicrobial susceptibility test (AST) results for the microorganisms causing BSIs can take 48 h or longer to obtain (18). Immediately after blood is collected for culture, empirical and often broad-spectrum antimicrobial therapy is initiated in patients suspected of having a BSI (19) and continued until the etiological agent is identified and AST results are available to target (tailor) therapy (20). Delay in microbial identification usually results in a lack of timely change from broad-spectrum antimicrobials to targeted therapy. Studies show that up to 40% of patients with BSIs, 50% of those with a health care-associated BSIs, and up to 70% of those with fungemia receive incorrect therapy during the empirical treatment period before the microbiology culture results are available (21–25). Incorrect continuous treatment with broad-spectrum antimicrobials can lead to drug toxicity, antimicrobial drug resistance, increased LOSs, and additional costs for patients and the health care system (26–31). Therefore, efficient communication of the results of Gram staining, microorganism identification, and ASTs that result in timely switches from empirical therapy to targeted therapy are essential for providing safe, effective, and efficient care of patients with BSIs (32, 33).

To reduce this important quality gap and potentially improve patient care, it is essential to identify effective practices that rapidly identify the microorganisms causing BSIs so that timely targeted therapy can be initiated. A systematic review of the effectiveness of rapid diagnostic practices in improving the timeliness of targeted therapy and outcomes in patients with BSIs has not been completed to date. The purpose of this review is to evaluate the evidence for the effectiveness of three rapid diagnostic practices in decreasing the time to targeted therapy for hospitalized patients with BSIs by applying the systematic review methods for quality improvement practices of the Centers for Disease Control and Prevention's (CDC's) Laboratory Medicine Best Practices Initiative (LMBP) and translating the results into evidence-based guidance (1).

PRACTICE DEFINITIONS

Five practices were initially considered for this review. Based on the available published manuscripts and gray literature, three rapid diagnostic practices were fully evaluated in comparison to conventional 24-h (or greater) microbiology culture with routine reporting methods for results issued after a positive blood culture is identified (i.e., after it “flags positive”). These practices are as follows: (i) rapid molecular techniques with additional direct communication of test results to clinicians or pharmacists to immediately confirm targeted therapy or switch patients from broad-spectrum or empirical therapy to targeted therapy based on the BSI agent, (ii) rapid molecular techniques without additional direct communication of test results (i.e., with only routine communication via an electronic medical record), and (iii) rapid phenotypic techniques with additional direct communication of test results to clinicians or pharmacists.

A “rapid” method was defined as a technique performed on positive blood culture bottles producing results in ≤ 8 h. This definition was based on the workgroup's decision to assess only rapid FDA-cleared assays and documented references to “rapid” diagnostic tests, defined by the CDC (34) and the World Health Organization (WHO) (35) as those that can be completed in ≤ 2 h, start to finish. This 8-h limit was selected by combining definitions with the workgroup's understanding of clinical laboratory workflow. In clinical laboratories, the workflow for even the most rapid of test methods, if most likely forced into some form of “batch” testing, is performed one or more times per 8-h work shift due to financial and/or operational considerations. Thus, for the purposes of this review, our practical working definition of a rapid diagnostic tool was one that delivers results in ≤ 8 h. Point-of-care tests, generally defined as those delivering results within ≤ 20 to 30 min of specimen collection, were not included, and notably, none existed for bloodstream infections at the time of the review or at the time of this publication. Rapid methods for mass spectrometry were originally included in the literature review but were excluded when none were identified by 2011.

Rapid molecular techniques that met the definition were identified and include the use of PCR and peptide nucleic acid fluorescent *in situ* hybridization (PNA-FISH). Rapid phenotypic techniques, adapted from their intended use to support rapid identification of bloodstream pathogens, were also identified and include tests such as those for tube coagulase (36, 37) and penicillin binding protein 2a (PBP2a) (36, 37), the bioMérieux Vitek 2 system (36, 37), the API 20E bacterial identification system (36, 37), thermonuclease testing (36, 37), and other applicable techniques (36, 37). Both molecular and phenotypic methods reviewed provide microbial characterization above that provided by routine generic Gram stain morphology, which is the historical reference standard (36, 37). The basis for the phenotypic and molecular methods and reports of their performance are published elsewhere (38–42).

For practices 1 and 3, the communication of test results involves directly reporting the results from the rapid identification technique to a responsible clinician or pharmacist who could take action to change therapy based on the laboratory result. These reporting efforts were defined as those that went above and beyond routine result reporting techniques, which included critical value reporting of the Gram stain results as well as reporting final microbial identification through the computer-based laboratory information system. Reporting rapid results generally involved phoning them in as soon as the

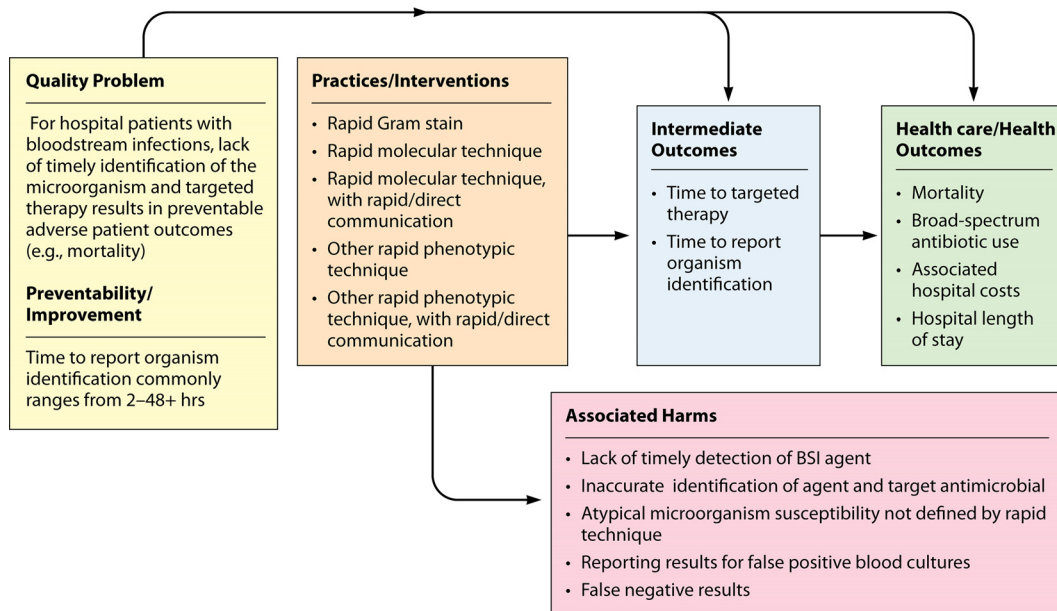


FIG 1 LMBP QI analytic framework: bloodstream infection evidence review question. For hospital inpatients who are admitted for, or are found to have, bloodstream infections (e.g., positive blood cultures), what practices are effective at increasing the timeliness of providing targeted therapy to improve clinical outcomes?

identifications or AST results for the samples were available (the possibility of reports to nursing or other health care staff as intermediate messengers was not excluded).

Two additional practices were considered in this review, but insufficient evidence, in the form of published articles or unpublished data, was found to evaluate their impact. They were rapid Gram staining (43) and rapid phenotypic techniques with routine communication of test results (4). For the purposes of this review, rapid Gram staining was defined as a situation in which Gram staining is performed and caregivers are informed of the results <1 h after the blood culture signals positive growth.

In summary, for the literature review, point-of-care testing with results in <15 min was applicable; Gram stain results were considered applicable between 15 and 60 min after a flag, and rapid results were defined as 1 to 8 h after a blood culture flag; anything that took longer than 8 h after a flag was not considered rapid for the purposes of this review.

METHODS

The evidence review for this work followed the CDC's LMBP "A6 cycle" systematic review methods for evaluating quality improvement practices, reported in detail elsewhere (1). This approach is derived from previously validated methods and is designed to evaluate the results of studies of practice effectiveness to support evidence-based best-practice recommendations. As in all A6 cycle reviews, a systematic review question is selected. Appendix 1 provides a list of the data elements of interest for the question posed for this review. Appendix 2 is a glossary of terms used during this process.

Using this method, a review coordinator and staff trained to apply the LMBP methods conducts the systematic review with guidance from an expert panel. The expert panel includes seven to nine members selected for their diverse perspectives and expertise on the review topic. At least one member is an expert in evidence

review methodologies. Appendix 3 lists the seven expert panel members participating in this review.

The expert panel reviews the results of the evidence review and drafts the evidence-based best-practice recommendations, which are approved by the LMBP Workgroup. The LMBP Workgroup is an independent, multidisciplinary group composed of 15 members, 13 invited and 2 *ex officio* representatives, from federal agencies (the Center for Medicare and Medicaid Services and the Food and Drug Administration) and with expertise in laboratory medicine, clinical practice, health services research, and health policy. A list of the members of the LMBP Workgroup is provided in Appendix 4.

ASK: REVIEW QUESTION AND ANALYTIC FRAMEWORK

The question to be answered by this evidence review is, "for hospital inpatients who are admitted for, or found to have, bloodstream infections (e.g., positive blood cultures), what practices are effective at increasing the timeliness of providing targeted therapy?" This review question is addressed in the context of the BSI analytic framework depicted in Fig. 1. The relevant population, intervention, comparison, and outcome (PICO) (1) elements are as follows.

- Population: all hospital inpatients who have a BSI
- Interventions:
 - Rapid molecular technique, with additional direct communication
 - Rapid molecular technique, with no additional direct communication
 - Rapid phenotypic technique, with additional direct communication
 - Rapid phenotypic technique, with no additional direct communication
 - Rapid Gram stain

- Comparison:
 - Conventional microbiology testing with phenotypic biochemical or antigenic methods
- Outcomes:
 - Time to targeted therapy is the primary outcome of interest
 - Secondary outcomes (as described below)

For the practices included in this review, “no additional direct communication” was defined as “routine communication” practices, such as those used for reporting of critical values. In contrast, several of the included studies introduced a supplemental rapid communication practice in concert with the adoption of the rapid testing method. These supplemental communication techniques are described below in the descriptive findings. For the latter studies, the effect of rapid testing could not be disentangled from the effect of the simultaneously introduced rapid communication. These results are therefore presented separately from the rapid-testing-only findings.

Although the time to initiate targeted therapy (directed specifically toward the microorganism causing the BSI) was considered to be the most direct (proximal) indicator of the effectiveness of these practices (and thus the primary outcome of interest), other outcomes were also included in this evidence review. Studies that did not include a time to targeted therapy outcome but which included the time to report an identification and/or AST results were included and considered to have a directly relevant outcome.

The expert panel also recommended using the findings for mortality for studies that did not report patient outcomes for either the time to targeted therapy or the time to report testing results. Although the most clinically relevant, mortality is a distal measure of the effectiveness of the rapid identification of BSI agents, as it is influenced by many factors beyond implementation of the rapid test practice. Study quality ratings were thus downgraded for studies contributing only a mortality outcome without statistically accounting for other characteristics of the patient or his/her treatment.

In addition to these findings, results for several other measures have been reported. For example, LOS is a commonly used outcome measure but was considered by the expert panel to be affected by too many medical and nonmedical factors to be considered a proximal measure of rapid-testing effectiveness. Results for these outcomes (i.e., LOS, broad-spectrum antimicrobial use, and cost) are reported in the individual study evidence summary tables provided in Appendix 5.

Practice definitions encompass a range of methods for microorganism identification by phenotypic or molecular practices. Evidence of effectiveness was considered across all microorganisms for a particular practice for which reagents were developed and applicable. Due to the limited availability of published and unpublished data, this approach was maintained for all included studies.

ACQUIRE: LITERATURE SEARCH AND REQUEST FOR UNPUBLISHED STUDIES

A comprehensive literature search was conducted to identify studies with measurable outcomes. With input from the expert panel and the assistance of a research librarian, a literature search strategy and terms were developed. In July 2011, we conducted a search

of three electronic bibliographic databases (PubMed, Embase, and CINAHL) and gray-literature sources and databases, including the International Network of Agencies for Health Technology Assessment (INAHTA), American Medical Association Clinical Practice Improvement and Patient Safety, American Hospital Association, American Medical Association Site Search, American Nurses Association, Canadian Thesis catalog, Canadian Institute for Health Information (CIHI), DART-Europe E-theses Portal, European Health Care and Hospital Federation—Activities, Google Blog search, HealthIT.hhs.gov NIHR Health Technology Assessment Programme, NLM Gateway, Open Gray, Proquest Dissertation Express, Scottish Intercollegiate Guidelines Network (SIGN), Surviving Sepsis Campaign, United Kingdom Clinical Research Network Study Portfolio, Virginia Henderson International Nursing Library (VHINL), and Cochrane database for English-language articles published between 1990 and 2011. Animal studies and non-English publications were excluded.

The search contained the following medical subject headings: bacteremia; bloodstream infection; time factors; health care costs; length of stay (LOS); morbidity; mortality; antimicrobial therapy; Meta-analysis; Review; Evaluation Studies, Clinical Nursing Research Costs; Cost analysis; Cost-Benefit analysis; Nursing; Diagnostic Techniques and Procedures; Diagnosis; Validation studies, Evaluation Studies, Comparative studies; technical report; PNA-FISH; peptide nucleic acids; economics; epidemiology; Outcome assessment; Bacterial Typing techniques; rapid molecular techniques, polymerase chain reaction (PCR); *in situ* hybridization, fluorescence; treatment outcome; drug therapy; patient care team; pharmacy service, hospital; hospital information systems; Gram stain; pharmacy service; mass spectrometry; Matrix-Assisted Laser Desorption-Ionization time of flight; phenotypic; and phenotype. We also included the key words cooperative behavior; agar; targeted therapy; rapid identification; rapid; Gram positive; Gram negative; reduce(ed); cost(s); pneumoslide; PBP2; tube coagulase; thermonuclease; Matrix-assisted laser desorption/ionization time of flight; MALDI TOF; blood culture; EMR; electronic reporting; call to provider; collaboration; pharmacy; laboratory; bacteria; yeast; ICU; and microbiology.

In addition to performing the electronic search, we made a request for unpublished quality improvement data through contacts of the expert panelists as well as e-mails to ASM’s ClinMicroNet listserv and the Association of Molecular Pathology’s champ listserv; in addition, a general request was posted to the LMBP website, now hosted at <http://wwwn.cdc.gov/futurelabmedicine/default.aspx>. The website provides instructions for submitting quality improvement data for LMBP reviews.

APPRAISE: SCREEN AND EVALUATE INDIVIDUAL STUDIES

At least two independent reviewers conducted an initial screening of titles and abstracts of published articles and reviewed full articles and unpublished data submissions to assess eligibility for inclusion for each study. The initial screening of titles and abstracts was used to exclude obviously ineligible studies from a full review. A study was included if it was considered likely to provide valid and useful information and met the PICO criteria previously discussed. Specifically, these inclusion criteria required that a study evaluate a specific intervention/practice included in this review with at least one finding for a relevant outcome measure (i.e., a change in the time to targeted therapy, a change in reporting time, and others noted previously) in a format which was useful for

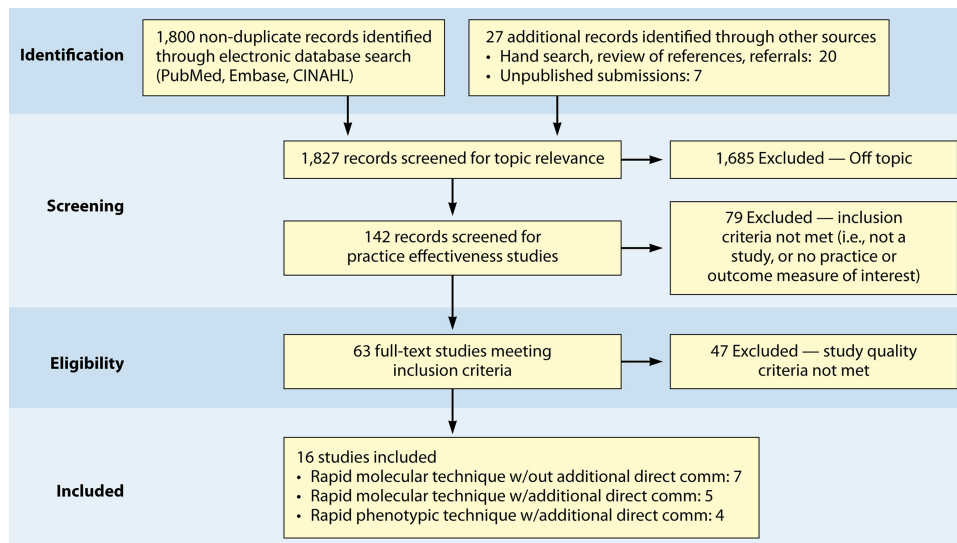


FIG 2 Systematic-review flow diagram. w/, with; comm, communication.

statistical analysis. Studies that did not meet the inclusion criteria (i.e., were not considered studies or did not include a practice of interest or an outcome measure of interest) were excluded from further review.

Published articles and unpublished quality improvement studies retrieved for the review were screened and evaluated by at least two independent reviewers to reduce subjectivity and potential bias. Differences in study quality ratings for each study were resolved through consensus. In addition, five microbiologists, including members of the expert panel and associated members of the American Society for Microbiology reviewed and evaluated the contributing studies. For eligible articles, information on study characteristics, interventions, outcome measures, and findings of the study were extracted using a standardized form. Each study was assigned one of three quality ratings (good, fair, or poor) based on the review of study characteristics and dimensions and assigned one of three effect size ratings (substantial, moderate, or minimal/none) based on the differences in relevant outcome measures after the implementation of the practice. Details on the rating process of individual studies can be found elsewhere (1). Studies that did not meet the LMBP study quality criteria (i.e., those with a fair or good quality rating) were excluded. Data from published studies and unpublished quality improvement projects that passed a full review were transformed to a standardized, common metric according to LMBP methods (1).

ANALYZE: DATA SYNTHESIS AND STRENGTH OF THE BODY OF EVIDENCE (META-ANALYSIS APPROACH)

The study quality and effect size rating results from eligible individual studies for each practice were aggregated into a practice body of evidence. When possible, an overall summary effect size was calculated to translate systematic review results into one of three evidence-based recommendations (recommended, no recommendation for or against, or recommended against). Both qualitative and quantitative analyses were used to assess the effect size, consistency, and patterns of results across studies (44) and to rate the overall strength of the body of evidence for practice effec-

tiveness (high, moderate, suggestive, and insufficient). Criteria for these ratings are described in greater detail elsewhere (1).

While recommendations are based on the entire body of evidence, effect sizes were calculated for all findings providing sufficient data to estimate the expected impact of a practice. Findings based on continuous data (e.g., the time to report) were standardized using the standardized difference in means (45, 46). Dichotomous findings (e.g., yes/no data, such as mortality) were summarized using the odds ratio (OR) (47).

The quantitative analysis uses the inverse-variance weighted effect sizes from conceptually similar individual studies to produce an overall average weighted effect size (grand mean) and 95% confidence interval (CI). The grand mean is estimated using a random-effects model, and it and the contributing estimates are presented in forest plots which graphically display each study's effect size so that they can be easily reviewed and compared. The I^2 statistic estimates the percentage of variability associated with between-study differences (45, 46).

In addition to there being an interest in evaluating the practices noted here, there was an interest in evaluating whether the effectiveness of rapid testing on the timeliness of the initiation of targeted therapy is related to the effectiveness of rapid testing on mortality. To do this, all effectiveness estimates of timeliness (d -scores) were regressed on all effectiveness estimates of mortality (log odds ratios). Although correlations do not inherently prove that causality exists, they are sufficient for estimating whether the two outcomes are likely related and determining whether there is support for the use of mortality as a proxy for timeliness.

RESULTS OF STUDIES

We identified a total of 1,820 nonduplicate bibliographic records and received 7 unpublished submissions covering the period of time between 1990 and July 2011. The reduction in the number of studies through the screening process is detailed in Fig. 2. The most common reason for exclusion of published or unpublished data was the fact that the publication was "off topic"; the second-most-common reason was a lack of applicable practice or out-

come data. A total of 16 eligible studies (12 published and 4 unpublished) were considered in the review of practice effectiveness (5 published and 2 unpublished for rapid molecular techniques, 3 published and 2 unpublished for rapid molecular techniques with additional direct communication, and 4 published for phenotypic techniques). Appendix 5 provides abstracted, standardized information and study quality ratings in evidence summary tables for the eligible studies.

There was insufficient evidence to include the practices of phenotypic techniques without additional direct communication and Gram staining in the systematic review evaluation. No studies examining the effectiveness of rapid phenotypic techniques without additional direct communication were located.

Note that the Gram stain technique was used as a routine microbiology test in all of the included studies to confirm the positive blood culture result from the automated continuous-monitoring system; however, only one publication on the use of rapid Gram staining which met the LMBP systematic review study criteria was identified (43). Thus, analytic methods could not be performed. The Barenfanger et al. study (43) is mentioned here to emphasize the potential advantage of rapid Gram staining and reporting of blood cultures as soon as they are flagged positive on the automated continuous blood culture systems. According to this one study, rapid Gram stain reporting has the potential to decrease the time to targeted antimicrobial therapy and decrease morbidity/mortality, the length of a hospital stay, and other associated hospital costs (43). Further studies of this practice are needed to more fully understand and evaluate the effectiveness of this technique. Evidence for the three remaining practices is described below.

Rapid Molecular Techniques without Additional Direct Communication

Seven eligible studies were found comparing rapid molecular techniques without additional direct communication with conventional microbiology practices with routine communication. These rapid molecular techniques allowed for direct detection and susceptibility testing of bloodstream infections from positive blood culture bottles. The studies included in the final analysis are summarized in Tables 1 and 2. The publication dates of these studies range from 2003 (48) to 2010 (49, 50). Two of the seven studies were originally unpublished (51; K. Stellrecht, M. Grifasi, E. Graffunder, and T. Lodi, unpublished data) (see Table A7 in Appendix 5), and the Frye et al. manuscript was subsequently published and is referenced here (51). Of the seven studies, three were rated “fair” (48, 50; Stellrecht et al., unpublished) (see Table A7 in Appendix 5) and two studies were rated “good” (49, 51). Two additional studies were rated “poor” (52, 53) and were excluded from consideration in this review. All five studies included in the practice body of evidence for this review used PCR molecular techniques to identify BSI agents (48–51; Stellrecht et al., unpublished) (see Table A7 in Appendix 5). Each of the PCR studies used a different technique. All of the studies were performed in the United States using adult inpatients in large (generally with >500 beds) academic teaching or tertiary-care medical centers.

Body-of-evidence qualitative analysis. The evidence of practice effectiveness for improving treatment timeliness by rapid molecular techniques without routine communication for hospital inpatients

indicates that treatment is inconsistent but often substantially faster than after standard testing (Table 2). One study (Stellrecht et al., unpublished) (see Table A7 in Appendix 5) provided results that could not be standardized. The weighted difference in median hours to the time of targeted therapy for this study was 14.7 h for the rapid molecular technique versus 22.6 h for conventional testing, which was rated as having a substantial effect size. Results for the remaining four studies could be standardized. The standardized differences in means (*d*-score) that were calculated for these four included studies ranged from 0.131 to -0.675 (with negative values favoring the rapid molecular technique over standard testing). The *d*-score for three of the four studies exceeded -0.6 , for a substantial effect size rating. Converting a *d*-score of 0.6 into the common-language statistic (54), a randomly selected rapid molecular test result will be reported faster than a randomly selected standard test result approximately 66.4% of the time.

Meta-analysis. The forest plot in Fig. 3 presents the meta-analysis effect size results for a rapid molecular technique without additional direct communication compared to standard testing for the four studies with standardized results in the body of evidence estimated using a random-effects model. The *d*-score confidence interval suggests that rapid molecular testing without direct communication is not significantly better in increasing timeliness than standard testing (average *d*-score = -0.422 ; 95% CI, -0.888 to 0.044 ; $P > 0.05$); however, there is significant heterogeneity in the estimates summarized ($Q = 18.24$, $P < 0.05$), with approximately 84% of the variability in results attributable to between-study differences ($I^2 = 83.55$) (54). The observed heterogeneity is caused by the work of Frye et al. (51), whose results favored the comparison practice. With the paper by Frye et al. (51) removed, the results of the remaining three studies for a rapid molecular technique are homogeneous ($Q = 0.043$, $P > 0.05$) and the overall improvement in timeliness from implementing rapid molecular testing is statistically significant (mean *d*-score = -0.634 ; 95% CI = -0.882 to -0.389 ; $P < 0.001$).

Rapid Molecular Techniques with Additional Direct Communication

There were five studies on the effectiveness of rapid molecular techniques with additional direct communication practice, which are summarized in Tables 3 and 4. Three of the studies were published (55–57) and two were unpublished (58; D. C. Gamage, D. P. Olson, N. N. Whitfield, L. H. Stickel, D. R. Johnson, and K. R. Matthais, unpublished data) (see Table A12 in Appendix 5). The Heil et al. data were subsequently published, and the report is referenced here (58). Three of the five studies utilized the PNA-FISH method on blood samples from bottles positive for culture as detected by continuous-monitoring culture systems. The PNA-FISH technique in these studies was used to identify *Candida* (58; Gamage et al., unpublished) (see Table A12 in Appendix 5) and two species of *Enterococcus* (*E. faecalis* and *E. faecium*) (56; Gamage et al., unpublished) (see Table A12 in Appendix 5). One study (55) using the GeneXpert real-time PCR platform identified methicillin-resistant *S. aureus* (MRSA). All studies were performed in large medical centers in the United States (55–57; Gamage et al., unpublished) (see Table A12 in Appendix 5). One study (55) was rated “good,” and four studies were rated “fair” (56–58; Gamage et al., unpublished) (see Table A12 in Appendix 5). The additional direct-communication

TABLE 1 Body-of-evidence summary of rapid molecular techniques without additional direct communication^a

Study (reference), quality rating, effect size	Populations/samples	Setting	Time period	Outcome/results
Parta et al. (50), fair, substantial	Posttest, patients tested by BC + Xpert <i>mecA</i> ($n = 58$), group 1 (4 Jan–15 July 2009) Pretest, patients tested by BC + GPCC ($n = 106$), group 2 (1 June–31 Dec 2008) Patients tested for MSSA (1 Jan–31 May 2008) using comparative test (48–72 h)	Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX	Group 1 (posttest), 4 Jan–15 July 2009 Group 2 (pretest), 1 Jan–31 Dec 2008	Time to indicated targeted therapy: MSSA drug therapy (mean time): group 1, 5.2 h ($n = 12$), vs group 2, 49.8 h ($n = 48$) ($P = 0.007$) MSSA drug therapy (median time): group 1, 0 h ($n = 12$), vs group 2, 48.5 h ($P = 0.004$) MRSA (mean time): group 1, 1.1 h ($n = 8$), vs group 2, 5.8 h ($n = 50$) ($P = 0.33$)
Hallin et al. (48), fair, moderate	35 adult inpatients suspected of having staphylococcal BSI by Gram staining and conventional culture tests vs direct PCR with 3 sets of primers for 16S rRNA, thermostable <i>nuc</i> , and <i>mecA</i>	Not provided; infectious disease specialists evaluated implementation of treatment	8 mo	Time to report indicated ID: <i>S. aureus</i> by PCR, 6 h 8 min (range, 4 h 50 min–7 h 30 min) <i>S. aureus</i> by conventional tests, 36 h 39 m (range, 27 h 35 min–51 h 1 min) CoNS, 49 h 16 min (range, 47 h 6 min–51 h 21 min) PCR results, supplied on avg 39 h earlier than conventional test results ($P < 0.01$)
Stellrecht et al., unpublished, fair, substantial	186 patients with GPC BSI, no. of cases, 136; multiplex PCR for <i>mecA</i> and <i>nuc</i> gene and BD Ohm to reduced Vanco therapy for MSSA BSI; no. of controls, 50; conventional ID testing and AST for MRSA and MSSA	Albany Medical Center, Albany, NY	1 Jan 2005 and 18 Apr 2007	Time to targeted therapy (median): MSSA, 18 h (PCR, $n = 72$) vs 37 h 26 min (comparator, $n = 25$) ($P = 0.35$) MRSA, 11 h 10 min (PCR, $n = 64$) vs 8 h 1 min (comparator, $n = 25$) ($P = 0.06$). (MRSA patients were already on Vanco)
Nguyen et al. (49), good, substantial	Pre-PCR, 65 samples; post-PCR, 94 samples; empirical vancomycin BCs positive for MSSA	Stanford Hospital; large academic center	Pretest Dec 2007–May 2008; posttest Dec 2008–May 2009	Time to targeted therapy: Vanco replacement, 2 (range, 1–18) days for post-PCR group vs 5 (range, 1–45) days for pre-PCR group ($P < 0.0001$)
Frye et al., unpublished, ^b good, minimal/none	Pretest for <i>S. aureus</i> , 68 samples; for CoNS, 66 samples; posttest for <i>S. aureus</i> , 58 samples; for CoNS, 52 samples; inpatients with positive BC were tested by Gram stain for GPCC and by a conventional test (Staph single-reaction PCR assay)	Two 500-bed tertiary medical centers	Pretest, 15 Jan 2009–14 Jan 2010; posttest, 15 Jan 2010–14 Jan 2011	Time to targeted therapy (mean [range]): Pretest for <i>S. aureus</i> , $n = 61$, 23.8 (0.2–74.7) h vs posttest, $n = 55$, 25.0 (0.5–91.3) h; difference (95% CI) = 1.2 (–5.1, 9.8) ($P > 0.1$) Pretest for MRSA, $n = 22$, 10.7 (0.22–24.72) h vs posttest, $n = 24$, 14.4 (0.67–36.88) h; difference (95% CI) = 3.7 (–1.8, 9.1) ($P > 0.1$) Pretest for MSSA, $n = 40$, 32.8 (0.27–96.1) h vs posttest, $n = 32$, 35.1 (0.52–98.48) h; difference (95% CI) = 2.3 (–10.5, 15.2) ($P > 0.1$)

^a BC, blood culture; GPC, Gram-positive cocci; GPCC, Gram-positive cocci in clusters; MSSA, methicillin-sensitive *Staphylococcus aureus*; ID, identification; CoNS, coagulase-negative *Staphylococcus*; Vanco, vancomycin; AST, antimicrobial susceptibility test.

^b Now published as reference 51.

TABLE 2 Body-of-evidence LMBP summary ratings for the rapid molecular technique without additional direct communication^a

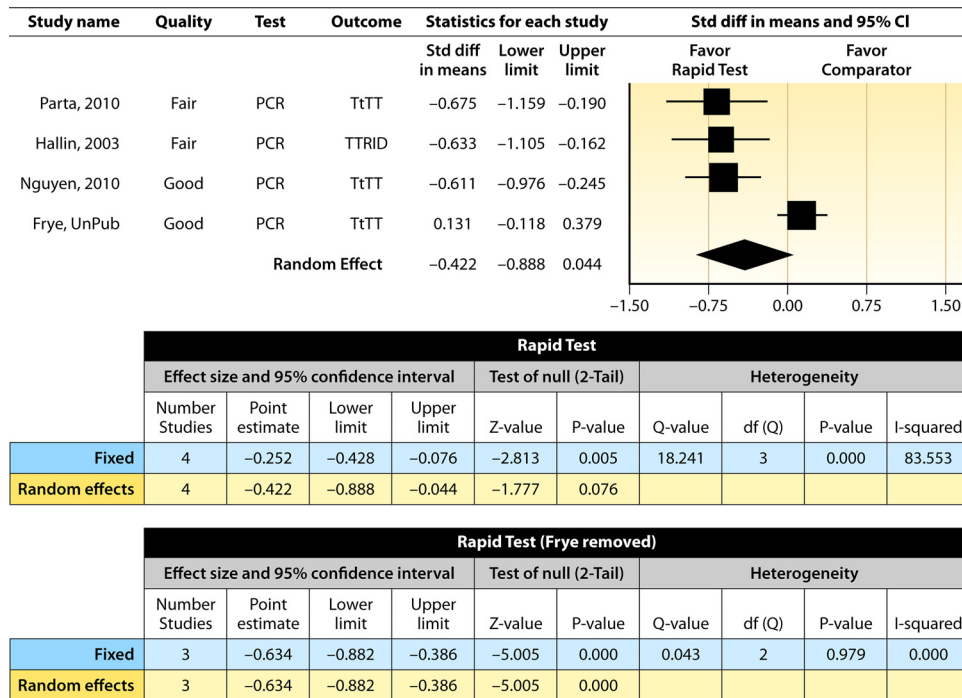
Study (reference)	Study quality rating	Effect size ratings
Parta et al. (50)	Fair	Substantial
Hallin et al. (48)	Fair	Substantial
Stellrecht et al., unpublished	Fair	Substantial
Nguyen et al. (49)	Good	Substantial
Frye et al., unpublished ^b	Good	Minimal/none

^a There was one study for which the quality rating was good and the effect size substantial, one study for which the quality rating was good and the effect size minimal or none, and three studies for which the quality rating was fair and the effect size substantial. There was no consistency among them, and the overall strength of the studies was low.

^b Now published as reference 51.

interventions for antimicrobial therapy switches were initiated by infectious disease pharmacists (55), laboratory clinical liaisons (57), an antimicrobial management team (56), laboratory staff calling results to infectious disease pharmacists (59; Gamage et al., unpublished) (see Table A12 in Appendix 5), and laboratory personnel paging on-call pharmacists, who then made a recommendation to a medical service based on the institution-specific antibiogram (58).

Body-of-evidence qualitative analysis. Primarily due to the “fair” quality of eligible studies, the strength of the evidence that timeliness of treatment in hospital settings is improved



Interpretation: Tested practice is not significantly better than comparator ($p < 0.05$); estimates are significantly different from each other. The heterogeneity is attributable to Frye (UnPub). With Frye removed, variation in the remaining results is attributable to sampling error and the practice is significantly better than the comparator.

FIG 3 Meta-analysis forest plot showing an analysis of rapid molecular techniques versus routine microbiological methods. The rapid molecular technique was without additional direct communication. Parta, 2010, see reference 50; Hallin, 2003, see reference 48; Nguyen, 2010, see reference 49; Frye, UnPub, Frye et al., unpublished (now published as reference 51); TtTT, time to targeted therapy; TTRID, time to report identification; Std diff, standard difference.

using rapid molecular techniques with additional direct communication compared to standard testing without direct communication is low (Table 4). Of the five studies identified, three provided results directly assessing the time to targeted therapy. The standardized difference in means (d -scores) for these studies ranged from -4.023 to -0.351 (with values less than 0.0 favoring a rapid molecular technique with direct communication over standard testing and standard communication). Two additional studies (57; Gamage et al., unpublished) (see Table A12 in Appendix 5) provided results documenting substantial reductions in mortality when rapid molecular testing with direct communication was implemented (OR = 0.425 [95% CI, 0.174 to 1.036] and OR = 0.576 [95% CI, 0.314 to 1.058], respectively).

Meta-analysis. The forest plot in Fig. 4A presents the meta-analysis of effect size results estimated using a random-effects model for a rapid molecular technique with additional direct communication compared to standard testing for the three studies with a standardized difference in means in the body of evidence. Combined, the d -scores for the three studies suggest that rapid molecular testing with direct communication significantly improves timeliness compared to standard testing (mean d -score = -1.483 ; 95% CI, -2.691 to -0.275 ; $P < 0.05$). Heil et al.'s (58) rather remarkable effect size (d -score = 4.023) creates considerable heterogeneity ($Q = 81.16$; $P > 0.000$). Removing the results of Heil et al. (58) returns a homogeneous distribution ($Q = 0.007$; $P > 0.05$) and a commensurately smaller, albeit still significant, improvement in the time-

liness of targeted therapy (mean d -score = -0.360 ; 95% CI, -0.530 to -0.190 ; $P < 0.001$). With the work of Heil et al. (58) included, a randomly selected rapid molecular test result with direct communication will be reported faster than a randomly selected standard test result approximately 85.3% of the time; excluding the work of Heil et al., the report will be faster approximately 60.1% of the time.

Two studies (57; Gamage et al., unpublished) (see Table A12 in Appendix 5) did not report a timeliness estimate but did provide mortality data (Fig. 4B). Combined, these studies show a significant and homogeneous reduction in mortality associated with rapid molecular testing combined with direct communication (mean OR = 0.523; 95% CI, 0.317 to 0.864; $P < 0.05$; $Q = 0.307$; $P > 0.05$).

Rapid Phenotypic Techniques with Additional Direct Communication

Information from the four included studies with evidence of the effectiveness of rapid phenotypic techniques for direct detection and susceptibility testing of bloodstream infections from blood culture bottles with additional communication compared to conventional microbiology practices is summarized in Tables 5 and 6. Studies for this practice include identification and susceptibility of a wide range of microorganisms and include specimens in addition to blood culture. The publication dates for these studies range from 1989 (60) to 2008 (61). The quality of all four studies for this practice was rated "fair" (60–63). Two studies were performed in large university medical centers (61, 63), one study was performed in a multisite teaching

TABLE 3 Body-of-evidence summary for rapid molecular techniques with additional direct communication^a

Study (reference), quality rating, effect size	Populations/samples	Setting	Time period(s)	Outcome/results
Heil et al., unpublished, ^b fair, substantial	Pretest group $n = 61$; posttest group $n = 21$; for patients with positive BCs, the first episode of candidemia/patient was analyzed; no statistically significant difference between groups	Not provided	9 mo	Mean time to targeted therapy (95% CI): Pretest, 2.3 days (1.4–3.2 days), vs posttest, 0.6 days (–0.01–1.16 days) ($P = 0.0016$)
Ly et al. (57), fair, substantial	Control group, 101 patients (no LCL); intervention group, 101 patients with LCL intervention); patients were blindly randomized 1:1; BC positivity and GPCC positivity were counted once	Washington Hospital Center (907-bed tertiary-care center), Washington, DC	7 mo	Mortality: Control group, 16.8% (17/101), vs intervention group, 7.9% (8/101) ($P = 0.05$)
Gamage et al., unpublished, fair, substantial	<i>Enterococcus</i> , pretest group $n = 198$; posttest group $n = 124$; 24/7 group $n = 138$; <i>Candida</i> spp., pretest group $n = 42$; posttest group $n = 44$; 24/7 group $n = 39$; enterococci were tested with blood culture bottles and Gram staining; the GPCPC and yeast pretest was phenotypic ID; the posttest was PNA-FISH	University of Arizona Medical Center, Tucson, AZ; tertiary-care academic center	Pretest period, Aug 2007–Aug 2008; posttest period, Aug 2008–Mar 2010; 24/7 period, Mar 2010–Mar 2011	Mortality: All patients with GPCPC, pretest group, 13.1% (26/198), vs posttest group, 7.6% (10/132) ($P = 0.15$) ICU patients with GPCPC, pretest group, 34.6% (19/55), vs posttest group, 15.6% (7/44) ($P = 0.04$) All yeast patients, pretest group, 26.8% (13/41), vs posttest group, 7.7% (3/39) ($P = 0.04$) Yeast patients from ICU, pretest group, 41.7% (10/24), vs posttest group, 5.9% (1/17) ($P = 0.01$)
Forrest et al. (56), fair, moderate	Pretest group $n = 129$; posttest group $n = 95$; all with hospital-acquired <i>E. faecium</i> or <i>E. faecalis</i> bacteremia	University of Maryland Medical Center; 600-bed tertiary-care teaching hospital	2005 (pretest); 2006 (posttest; tested by PNA-FISH)	Median time to targeted therapy (range): Patients with <i>E. faecalis</i> pretest group ($n = 64$), 0 (0–5.3) days, vs posttest group ($n = 48$), 0.3 (0–6.5) days ($P = 1$) Patients with <i>E. faecium</i> pretest group ($n = 65$), 3.1 (0–9) days, vs posttest group ($n = 47$), 1.3 (0–4.3) days ($P < 0.001$).
Bauer et al. (55), good, moderate	Adult inpatients BC positive for <i>S. aureus</i> , pretest group = 74, posttest group = 82; MicroScan Walkaway test and cefoxitin disk vs Xpert PCR with intervention (infectious disease pharmacist) for therapy switch	Ohio State University Medical Center, 1,150-bed tertiary-care facility (Columbus, OH)	Prior to 1 Sept 2008–31 Dec 2008; after 10 Mar 2009–30 June 2009	Time to targeted therapy: MSSA group, time required to switch vancomycin to cefazolin or nafcillin; pretest group, 3.6 days, vs posttest group, 2 days ($P = 0.002$) MRSA group, time required to switch vancomycin to daptomycin; pretest group, 10 days, vs posttest group, 4.5 days ($P = 0.15$)

^a LCL, laboratory/clinician liaison; GPC, Gram-positive cocci; GPCC, Gram-positive cocci in clusters; GPCPC, Gram-positive cocci in pairs and chains; 24/7, monitored 24 h per day, 7 days per wk; ICU, intensive-care unit.

^b Now published as reference 58.

hospital laboratory setting (62), and the fourth study was performed in a large hospital (60). Two studies were performed in The Netherlands (61, 62), and two were performed in the United States (60, 63). Additional direct communication interventions were initiated by an

infectious disease fellow making recommendations directly to the physician in charge (60), by laboratory staff immediately phoning identification and antimicrobial results to an infectious disease consultation service (61) or directly to physicians who had requested the

TABLE 4 Body-of-evidence LMBP summary ratings for the rapid molecular technique with additional direct communication^a

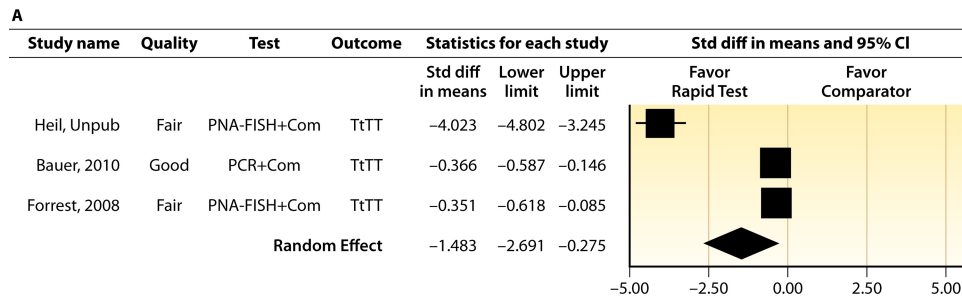
Study (reference)	Study quality rating	Effect size rating
Heil et al., unpublished ^b	Fair	Substantial
Ly et al. (57)	Fair	Substantial
Forrest et al. (56)	Fair	Moderate
Gamage et al., unpublished	Fair	Substantial
Bauer et al. (55)	Good	Moderate

^a There was one study for which the quality rating was good and the effect size moderate, three studies for which the quality rating was fair and the effect size substantial, and one study for which the quality rating was fair and the effect size moderate. There was no consistency among them, and the overall strength of the studies was low.

^b Now published as reference 58.

analysis (63), and by a clinical microbiologist phoning clinically relevant information and treatment advice, if necessary, to the attending clinician (62).

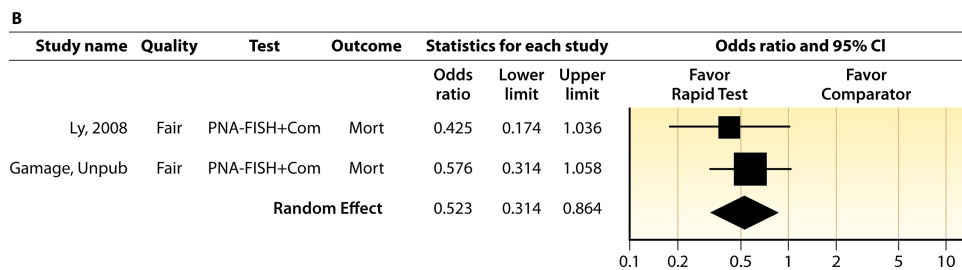
Body-of-evidence qualitative analysis. Evidence of effectiveness for improving treatment timeliness using rapid phenotypic techniques with additional direct communication indicates generally substantial improvement over standard testing practices. All four studies were of fair quality, and the three studies assessing time to targeted therapy each reported “substantial” improvement in timeliness (61–63), resulting in an overall low strength of evidence in hospital settings. Trenholme et al. (60) reported a moderate



Rapid Test with Communication										
Effect size and 95% confidence interval				Test of null (2-Tail)			Heterogeneity			
	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	3	-0.527	-0.693	-0.361	-6.217	0.000	81.155	2	0.000	97.536
Random effects	3	-1.483	-2.691	-0.275	-2.407	0.016				

Rapid Test with Communication (Heil removed)										
Effect size and 95% confidence interval				Test of null (2-Tail)			Heterogeneity			
	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	2	-0.360	-0.530	-0.190	-4.152	0.000	0.007	1	0.932	0.000
Random effects	2	-0.360	-0.530	-0.190	-4.152	0.000				

Interpretation: Tested practice is significantly better than comparator ($p < 0.05$); estimates are significantly different from each other. Removing Heil, the tested practice is still significantly better than the comparator ($p < 0.05$); estimates are not significantly different from each other.



Rapid Molecular Technique, with Direct Communication (Mortality)										
Effect size and 95% confidence interval				Test of null (2-Tail)			Heterogeneity			
	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	2	0.523	0.317	0.864	-2.529	0.011	0.307	1	0.580	0.000
Random effects	2	0.523	0.317	0.864	-2.529	0.011				

Interpretation: Tested practice is significantly better than comparator ($p < 0.05$); estimates are not significantly different from each other.

FIG 4 (A) Meta-analysis forest plot of rapid molecular techniques, with additional direct communication, versus routine microbiological methods. Heil, Unpub, now published as reference 58; Bauer, 2010, see reference 55; Forrest, 2008, see reference 56; Com, comparator. (B) Meta-analysis forest plot of a rapid molecular technique, with additional direct communication, versus routine microbiological methods of interpretation. Ly, 2008, see reference 57; Gamage, Unpub, Gamage et al., unpublished; Mort, mortality.

TABLE 5 Body-of-evidence summary for the phenotypic technique with additional direct communication^a

Study (reference), quality rating, effect size	Populations/samples	Setting(s) (description)	Time period(s)	Outcome/results
Kerremans et al. (61), fair, substantial	1,498 inpatients with positive culture growth from tested body fluid; <i>n</i> = 746 for practice method and <i>n</i> = 752 for comparator method; bacteria and fungi evaluated	Erasmus Medical Center (1,200-bed tertiary-care university center), The Netherlands (laboratory was active for 24/7 consultation service by medical microbiologists and infectious disease specialists; weekend lab hours)	2 yr	Time to targeted therapy, practice method vs comparator method (no. of switches to appropriate therapy): On day of randomization, 90 switches vs 60 switches (<i>P</i> = 0.006) Day 2 after randomization, 42 switches vs 24 switches (<i>P</i> = 0.019)
Doern et al. (63), fair, substantial	Inpatient practice group (rapid AST) <i>n</i> = 273, comparator group (overnight AST) <i>n</i> = 300; patients were tested for <i>S. aureus</i> , CoNS, <i>Acinetobacter</i> spp., and <i>Enterobacteriaceae</i> ; included infections other than BSIs	University of Massachusetts Medical Center (tertiary-care, teaching center)	1 yr	Time to targeted therapy: By RAST = 16.3 h vs by ONAST = 31.2 h (<i>P</i> < 0.0005)
Bruins et al. (62), fair, substantial	1,883 inpatients with confirmed bacterial infections from <i>Enterobacteriaceae</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus</i> spp., and <i>Enterococcus</i> spp.; tested by rapid Vitek 2 vs API test overnight and conventional AST (control group)	Isala Klinieken (multisite 1,100-bed tertiary-care teaching hospital), Zwolle, The Netherlands	SP1, Sept–Nov 2000; SP2, Dec 2000–Feb 2001; SP3, Mar–June 2001	Median time to targeted therapy (IQR) based on sample arrival time and first change in therapy: SP2, rapid Vitek 2, 27.0 h (7.5–86.5 h) vs API overnight conventional, 49.0 h (13.0–94.0 h) (<i>P</i> = 0.028) The differences between SP1 and SP3 were not significant
Trenholme et al. (60), fair, moderate	Direct Vitek ID group <i>n</i> = 110 vs AST group <i>n</i> = 116 for conventional culture; various organisms were included; inpatients with BC positivity were randomly assigned to the study	Not provided	11 mo	Time to report ID for rapid Vitek 1 (range) vs conventional 24-h culture methods: Gram-positive cocci ID, 10.6 h (4–15 h); AST, 6.6 h (4–10 h) Gram-negative rod ID, 5.8 h (4–18 h); AST, 5.9 h (4–10 h) Overall ID, 8.8 h vs 48 h; AST, 6.4 h.

^a RAST, rapid antimicrobial susceptibility testing; ONAST, overnight antimicrobial susceptibility testing; SP1, -2, and -3, study phases 1, 2, and 3, respectively; IQR, interquartile range.

improvement in the time to report an identification. Two of the four studies, those of Kerremans et al. (61) and Doern et al. (63), provided significant positive results in improving timeliness that could be standardized (*d*-scores, -0.270 and -0.146 , respectively).

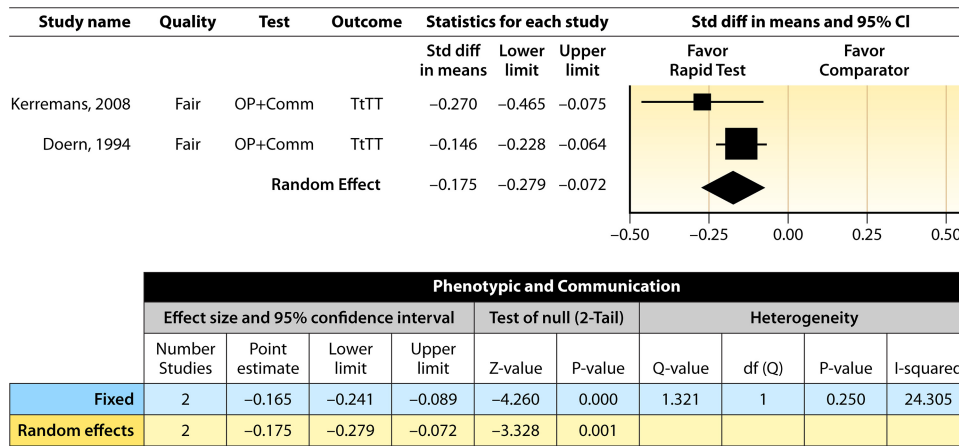
TABLE 6 Body-of-evidence LMBP summary rating for the phenotypic technique with additional direct communication^a

Study (reference)	Study quality rating	Effect size rating
Kerremans et al. (61)	Fair	Substantial
Doern et al. (63)	Fair	Substantial
Bruins et al. (62)	Fair	Substantial
Trenholme et al. (60)	Fair	Moderate

^a There were three studies for which the quality rating was fair and the effect size substantial and one study for which the quality rating was fair and the effect size moderate. There was consistency among them, and the overall strength of the studies was low.

Meta-analysis. The forest plot in Fig. 5 presents the meta-analysis effect size results for rapid phenotypic techniques with additional direct communication compared to standard testing for the two studies with standardized time-to-targeted-therapy outcome measures estimated using a random-effects model. A significant and homogeneous grand mean suggests that rapid phenotypic techniques with direct communication likely improves the timeliness of targeted therapy (average *d*-score = -0.175 ; 95% CI, -0.279 to -0.072 ; *P* < 0.001). Converting these to the common-language statistic suggests that a randomly selected rapid phenotypic test result with additional direct communication will result in targeted therapy faster than a randomly selected standard test result approximately 54.9% of the time.

Impact on mortality. There is interest in whether the implementation of a rapid technique and communication practice(s) reduces mortality. Five studies included in this review provided



Interpretation: Tested practice is significantly better than comparator ($p < 0.05$); estimates are not significantly different from each other.

FIG 5 Meta-analysis forest plot of phenotypic techniques, with additional direct communication, versus routine microbiological methods. Kerremans, 2008, see reference 61; Doern, 1994, see reference 63.

estimates for both the time to targeted therapy after implementing a rapid identification technique (with or without additional direct communication) and mortality (51, 56, 61–63). As noted previously, the effectiveness estimates of timeliness to targeted therapy from these studies (d -scores) were regressed on the effectiveness estimates of mortality (log odds ratios). Figure 6 shows the resulting regression. Note that one study by Heil et al. (58) was left out of the analysis, as its estimate on timeliness to targeted therapy is an outlier and significantly different from the other reported results. The random-effect results for this regression showed an r of 0.6762 ($P = 0.3366$; $r^2 = 0.4572$). Although a strong correspondence between the timeliness of targeted therapy and mortality can be observed, given the evidence available, the relationship fails to reach significance. Although it seems likely that the two outcomes are associated, that relationship is yet to be proven.

ADDITIONAL CONSIDERATIONS

This section addresses additional considerations for implementing molecular and phenotypic methods for rapid identification

and susceptibility testing with or without direct communication practices for early intervention and administration of targeted therapy to patients with BSIs.

Applicability

All studies included in this review were conducted on adult inpatients in large (generally >500 beds) academic teaching or tertiary-care medical centers, but observed improvements in times to targeted therapy may be generalizable to other health care settings. Studies in this review included a variety of settings, such as a Department of Veterans Affairs Medical Center and academic tertiary-care centers (50, 55, 56, 59). Study institutions with practices of rapid molecular techniques of PCR and PNA-FISH without additional direct communication practices had routine standards of communication in place similar to those typically found in most hospitals to confirm and switch appropriate antimicrobial therapy for patients with BSIs (48–50). Some sites appeared to have efficient communication without additional direct methods (49) based on described outcome results (Fig. 3). Hospitals implementing the practices of rapid molecular techniques or pheno-

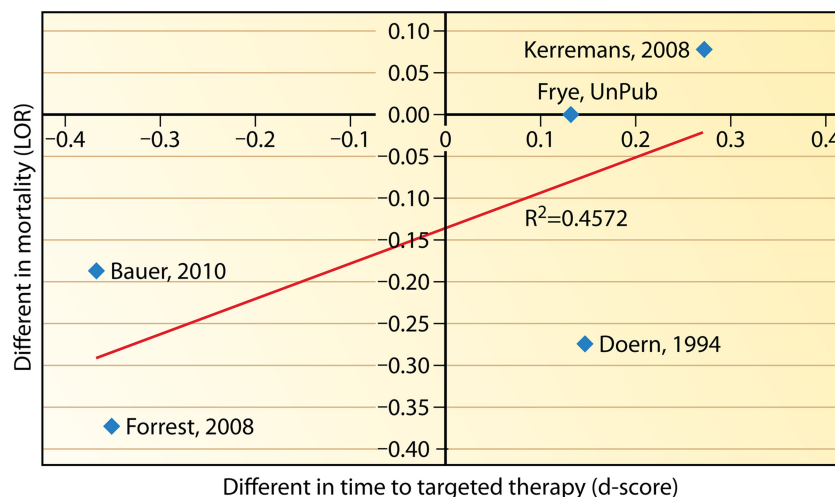


FIG 6 Regression of the effectiveness estimates of mortality (log odds ratios [LOR]) versus effectiveness estimates of timeliness to targeted therapy (d -scores).

typic techniques with additional direct communication included multidisciplinary teams with an infectious disease physician(s) and infectious disease pharmacists, research data managers (55), on-call pharmacists (58), and a laboratory/clinician liaison (57), which were essential to the practice.

Associated Harms

Although not identified in the evidence base, one of several hypothetical scenarios may suggest potential harm from the use of rapid identification techniques. Harms include the lack of timely and accurate detection of a BSI agent, despite rapid testing of positive blood culture bottles. In this scenario, the gains of the rapid testing and reporting would be nullified by the fact that the rapid intervention failed to identify the pathogen; therefore, additional laboratory costs would not be offset by a reduction in nonlaboratory costs. Risks of antimicrobial de-escalation, based on a negative rapid result, may exist during the time interval between the rapid result and the time at which the traditional culture and phenotypic methods produce a final identification and AST results. Furthermore, inaccurate identification of the microorganism might lead to inappropriate and ineffective changes in antimicrobial therapy, which might have significant repercussions on patient health and care if the therapy change is not warranted.

Likewise, a small proportion of blood cultures will yield more than one pathogen per bottle, resulting from infection with more than one pathogen or identification of a pathogen mixed with a typical skin contaminant. In this scenario, if rapid methods were not able to detect or discriminate between multiple pathogens, the outcome would be similar to that of the false-negative result described previously. This harm is partially mitigated by the fact that none of the assays promote rapid testing alone, without the use of a Gram stain, which can help distinguish between some pathogens in mixed infections. Furthermore, risks are limited by the subculture of the blood culture bottles, as subculture can more accurately identify mixed infections than a Gram stain alone. The implications of rapid testing methods described here may change if mixed infections become more common. Routine methods are still the definitive reference standard, and any discrepancies between a rapid method and the definitive culture result should be closely monitored; if antimicrobial therapy was inappropriately altered based on the rapid result, each instance would be reported as a potential patient safety risk.

A second harm may occur if the BSI-causing microbes that were identified by the rapid technique do not behave according to the respective institutional antibiogram. The use of an institution-specific antibiogram to guide therapy after rapid microbial identification to the genus or species level cannot account for exceptions and unforeseen mutations causing atypical susceptibility that the rapid technique cannot define. This circumstance might place patients with BSIs at risk until a final AST report is issued. Of note, this harm is implicit in all rapid methods upon which antimicrobial therapy is based and is also implicit in empirical therapy regimens.

Detection of bloodstream infections by molecular or phenotypic methods also includes the possibility of reporting results for false-positive or contaminated cultures and false-negative results due to insufficient growth in the blood culture itself. Rapid reporting of results by rapid molecular or phenotypic methods may give physicians a false sense of accuracy, causing them to overlook the basic limitations inherent in the blood culture process itself. While

false-positive blood culture results are likely to be identified sooner with rapid methods and add value to differential diagnoses, false-negative results must be mitigated by clinical evidence, since some of these organisms do not grow in standard blood cultures without selective culture medium requirements or special growth conditions. False-negative results may also be due to a lack of sensitivity in the test system to detect the low density of some microorganisms.

Additional Benefits

Studies reviewed suggest beneficial outcomes (decreasing mortality) associated with rapid molecular and rapid phenotypic techniques with or without additional direct communication (17, 52, 55–58; Gamage et al., unpublished) (see Table A12 in Appendix 5) and length of hospital stay (49, 55, 58) in addition to reducing the time to targeted therapy in patients with BSIs. One study showed that PCR surveillance for MRSA in a small community hospital was associated with decreasing the length of stay by 9.3% in the intensive care and critical care units in 2009 (D. Uettwiller-Geiger, unpublished data) (see Table A15 in Appendix 5). Studies reviewed also indicated that the time for the laboratory to report the identification of the microorganism causing the BSI was reduced when rapid molecular or phenotypic techniques were used (17, 48, 51, 56, 61). Several studies also documented that there was reduced use of broad-spectrum antimicrobials when rapid molecular techniques were employed, even in the absence of additional direct communication practices (49, 50, 53, 56, 59). Studies using rapid molecular or phenotypic techniques with additional communication also showed reductions in the use of broad-spectrum antimicrobials (55, 60, 61). Across all of these studies, reductions in the defined daily dose of antimicrobial medications ranged from 20 to 60% with the implementation of the practice.

Economic Evaluation

Decreasing the time that it takes for BSI microorganism identification and an AST result is commonly considered likely to reduce health care costs for both patients and institutions by reducing the time to appropriate targeted therapy. No economic evaluation studies that comply with guidelines for full economic evaluation (64–66) were found for the rapid testing techniques evaluated in this review. Direct medical costs are impacted by the patient's length of hospital stay, repeated use of laboratory testing or other diagnostic procedures, use of broad-spectrum antimicrobials, use of targeted antimicrobial therapy, and other pharmaceutical costs (28, 57).

Several studies reported a decrease in health care expenses after implementing rapid testing (55, 57, 59, 63; Uettwiller-Geiger, unpublished; Gamage et al., unpublished) (see Table A15 in Appendix 5 and Table A12 in Appendix 5), while others report decreased costs for antimicrobial agents (52, 62) and the total antifungal costs per patient (59). However, the cost reductions reported in these studies do not account for any additional costs associated with implementing rapid testing or costs and benefits associated with nonmedical costs (e.g., patient and caregiver time). Providing rapid testing may require additional laboratory space and additional staffing for both testing and direct communication. Other cost considerations that cannot be appropriately addressed are related to batching of tests, which occurred in most studies to make more efficient use of laboratory resources and reduce overall costs of testing.

Feasibility of Implementation

Implementation of the practices discussed in this review may be affected by specific hospital environments, laboratory settings, staff competencies, specimen volume, budget considerations, and the ability to provide active notification of test results to clinicians or pharmacists who will provide early antimicrobial interventions and appropriate therapy for patients with BSIs (19, 67). Implementing any new test into a microbiology laboratory or new practice in a hospital setting often encounters resistance due to efforts to control budgets related to reagents, human resources, and other factors (17, 28, 60, 61). Selection of an appropriate laboratory technique that best suits an institution often depends on making a business case, demonstrating potential quality outcomes or cost-effectiveness metrics (68).

A variety of different phenotypic and molecular techniques were utilized in the studies evaluated in this review; however, most of the studies in this review involved molecular tests performed in large university or tertiary-care centers. A number of the techniques have the capacity to identify a range of microorganisms directly from blood culture bottles determined to be positive for bacteria or yeasts (53, 55, 56; Gamage et al., unpublished) (see Table A12 in Appendix 5). The hands-on times, test turnaround times, costs, and types of reagents, as well as technical skills required to perform the test, varied among these different techniques. A single PNA-FISH test process was described and used with different PNA probes and was said to be less expensive and simpler to perform (not requiring special laboratory space) than a number of different PCR procedures with which different equipment, reagents, skill levels, laboratory space, and costs were associated (48–50, 52, 54, 55, 69).

Test sensitivity and specificity are important considerations in determining feasibility for implementing a new diagnostic laboratory procedure. Studies in this review for PNA-FISH and PCR methods provided 95% or greater sensitivity and specificity for detection of the genetic targets (16, 48, 51, 52, 54, 57, 59). A potential advantage of PCR over PNA-FISH is that PNA-FISH requires at least 10^4 organisms/ml in blood for detection (70), while the limits of detection for PCR are typically, but not always, lower (70–72). Since microbial genetic targets are amplified in PCR, it should be able to detect organisms present at lower microbial densities. A disadvantage of PCR is related to primer specificity and competitive inhibition, which can occur when one target at higher density limits the amplification of the genetic target at lower density. There is no competitive inhibition with PNA-FISH; each microbe can freely bind with a probe on its own and can be visualized independently by fluorescence microscopy. Rapid phenotypic tests have an organism density requirement similar to that of PNA-FISH for appropriate levels of detection and accuracy.

An important aspect of any rapid testing method is to ensure that test results reach the clinician in a timely manner with specific interventions that might improve relevant patient outcomes. For the studies that implemented practices with additional direct communication, various staff that could quickly act on results and affect interventions were needed. For example, studies by Forrest et al. (56) required a hospital-based antimicrobial management team which consisted of a full-time infectious disease pharmacist and an infectious disease physician who devoted 25% of his/her time to antimicrobial stewardship. These types of staff members and teams may not be readily available in all hospitals.

FUTURE RESEARCH NEEDS

The findings of this systematic review highlight the limited number of good-quality studies evaluating the impact of rapid testing of the microorganisms causing BSIs on reducing the time to targeted therapy for hospitalized patients. For those on-topic quality improvement studies that were conducted and reviewed but not included in the body of evidence, there are a number of reasons they were not eligible for this review. For some, the information provided was insufficient to allow an estimate of the effect of the practices of interest. For example, some studies reported a percentage improvement in timeliness but did not specify the value on which the improvement was based. For others, reported outcomes were only indirectly attributable to the practice (e.g., LOS, broad-spectrum antimicrobial use). While these outcomes may be affected by reduced times to targeted therapy, several other factors also influence these outcomes. The list of proposed study and reporting guidelines in Appendices 1 and 6 can be used to outline the elements recommended for future studies that aim to address the question presented in this systematic review with the rigor required to meet the systematic review inclusion criteria; one should also take into consideration the limitations of the studies identified for this review. Elements of Appendix 1 are discussed in detail below.

Most publications considered for this systematic review did not provide patient or clinical outcome data as a result of the rapid molecular or phenotypic practice(s) performed and were therefore not included in the analysis. Future studies should strive to obtain information on patient-centered outcome results and also to include the most-proximal outcome measures (such as time to targeted therapy and time to report identification results) such that the direct effect of implementing a particular practice may be assessed.

Many of the studies evaluated had small sample sizes, sometimes as few as 30 patients, from which to draw conclusions. Such small sample sizes limit the precision of results and reduce the likelihood that findings are applicable across a larger population (73). It is important that future studies select a sufficiently large sample size to enhance the accuracy and precision of the results observed.

Most of the studies reviewed lacked sufficient information on important study details to meet the inclusion criteria for LMBP systematic review. Had additional information been provided, it is possible that it would have improved study quality ratings. Future studies should include detailed information on topics such as the facility and study setting, sample population description and size, numeric ranges and standard deviations (SD) of results (i.e., not only arithmetic means), detailed descriptions of the comparator and intervention practice, information describing the staff and resources needed to implement the practice, and descriptions of changes in any ancillary practice, procedures, or other health care interventions that may bias study findings. As LMBP systematic reviews focus on the preanalytic and postanalytic phases of testing rather than the analytic phase (1), future studies should identify, address, and discuss the patient outcome quality gap that the laboratory practice is designed to improve.

One hypothesizes that decreasing the time to initiating targeted therapy in patients through the use of rapid molecular or phenotypic techniques in turn leads to lower morbidity and decreased rates of mortality, further supporting the use of (and costs associ-

ated with) such practices. However, as discussed previously, limited data were identified in this review to support this hypothesis. We need studies that collect both the immediate and longer-term outcome data necessary to test these relationships and conduct the analyses required to confirm that observed improvements in patient outcomes are attributable to changes in laboratory practices. More research is also needed to encompass the impact of varied hospital settings, such as small or nonacademic institutions, to document the effectiveness of rapid molecular and phenotypic techniques in different settings. A better understanding of how batching and other such routines for testing samples is needed and should also be considered for inclusion in upcoming studies.

Cost-related results should also be reported, based on quality standards for economic evaluations that would make the results meaningful and potentially generalizable and allow for comparisons across studies. A full economic evaluation (64–66) is beyond the scope and the funding of this review, and the concept is being considered for future reviews. Economic evaluation is a process completely different from that of the LMBP; it is worthwhile, but it does not correspond to the expertise of the LMBP team at this time and is not the purpose of the LMBP question. Guidance on cost information to consider for inclusion in future studies is provided in Appendices 1 and 6.

The body of evidence presented in this review shows that there are not sufficient good-quality studies on any one molecular or phenotypic technique to evaluate the technique's effectiveness alone. Further research on individual techniques and on the effectiveness of these techniques on specific microorganisms is needed. Clearly, more investigation needs to occur as part of the ongoing A6 cycle and the "assess" phase begins anew. While the A6 process does not have accommodations for modifying the original systematic review process and meta-analysis, which generally takes over 1 year to complete, it does accommodate a literature refresh process, which uses the original search terms to identify publications that may fit criteria between the time of the review and the time of manuscript submission. Another full systematic review began again in September 2015. The ongoing process by which the rereview should occur is under development by the CDC and ASM to determine factors that will trigger repeating the entire A6 cycle, including newly designed metrics to describe the uptake of guidelines across the laboratory community. Originally, the CDC felt that the process would occur every 5 years, but for the BSI project, that rereview will occur immediately, completing the A6 process and beginning it anew immediately after this paper went into production.

LIMITATIONS

This review includes more studies on molecular techniques than it does on traditional phenotypic test procedures commonly used in clinical or diagnostic laboratories. Most molecular procedures can be completed with a turnaround time of 2 to 3 h, but in most studies, turnaround times may be higher, as the tests were batched and performed once, twice (52, 53, 55–57), or three times per day (Gamage et al., unpublished) (see Table A12 in Appendix 5). The primary reason for batching tests appears to be related to a higher cost per test with lower test volume due to additional quality control requirements (49, 54) and limited staffing of medical laboratory scientists during off-shift laboratory work hours (50). Batching tests decreases the benefit of rapid test turnaround times, since delays in performance of the test also delays the reporting of test

results to clinicians and hence the opportunity to change from empirical to targeted therapy.

Although some rapid techniques can provide test results in approximately 1 h, timely evaluation of specimens is lacking when technical staff are not available to perform the rapid identification test (43). When rapid test results were available, additional direct communication for antimicrobial intervention from broad-spectrum to targeted therapy was sometimes not available (53); therefore, the true impact of rapid testing may be underestimated.

Several studies were based on small samples (48, 50, 51, 55, 58) and were performed in a single center (55, 56, 59). Molecular practices, such as PCR and PNA-FISH, were performed in large academic tertiary-care medical centers with technologists experienced in molecular techniques (50, 52, 56, 59), which may not be representative of other hospital settings.

Most studies in this review focused on distinguishing methicillin-resistant *S. aureus* from non-methicillin-resistant *Staphylococcus* species other than *S. aureus* (49, 53, 57, 59). A few studies evaluated blood cultures for *Enterococcus faecalis* and *E. faecium* (56, 62; Gamage et al., unpublished) (see Table A12 in Appendix 5). The limited number of microbes evaluated is notable, in that not all microbes may be associated with treatment algorithms that would warrant the costs or efforts for their rapid identification.

Most of the studies reviewed used a before/after or pre/postintervention study design. Because of the uncontrolled nature of this quasi-experimental study design, there may have been unmeasured factors that changed between study periods that account for or influence the study results. In many studies, patients were analyzed retrospectively, creating the potential for an information bias in pretest/posttest groups (28, 51, 53; Stellerecht et al., unpublished) (see Table A7 and Appendix 5). Despite this potential design effect, it is recognized that for practical reasons, randomized control clinical trials are beyond the scope of typical laboratory quality improvement studies.

Some of the outcome measures attributed to this topic are proximal measures of effectiveness of rapid identification practices, providing more-direct information on the effectiveness of a given practice (e.g., time to targeted therapy, time to report identification results). Other outcome measures are considered more distal, having multiple steps between the implementation of the practice and the outcome measure itself (e.g., length of stay and mortality).

While the time to report the identification results is considered the most direct measure of the effect of rapid testing, because of the many studies using batch testing or other factors influencing the reporting of test results, the possible improvement in time to targeted therapy reported in this review may be understated. In addition, since it is not uncommon for health care facilities to report blood culture results to nursing staff as an intermediate step before the physician sees the results, our work may include a reporting bias, since none of the publications analyzed reported nursing as their primary point of contact.

Most phenotypic and some molecular techniques in this review used multiplex systems designed to identify and provide susceptibility testing for a wide range of bacteria, including *Staphylococcus* species other than *S. aureus* and/or Gram-negative bacilli. Some *Enterobacteriaceae*, nonfermenting Gram-negative bacilli, and *Staphylococcus* species took longer to identify than other organisms. A longer time was also required for multiplex molecular

techniques, and these factors had some effect on the test turnaround time for identification. Tests were generally batched, and additionally, samples other than blood were included in statistical calculations, as most studies also collected urine, pus, or spinal fluid and often did not separate the findings based on collected specimens.

The LMBP systematic review methods are consistent with practice standards for systematic reviews (1), but all such methods include subjective assessments at multiple points that may produce bias. Rating study quality depends on consensus assessments that may be affected by such things as rater experience and the criteria used. As is the case with most systematic reviews, publication bias must be considered despite the inclusion of unpublished studies, which may help to mitigate that bias. One of the strengths of the LMBP process is the inclusion of nonpublished data to help reduce publication bias. The restriction to English-language studies to satisfy the requirement of multiple reviewers for each study may also introduce bias.

It is commonly known that few if any molecular assays worldwide will totally escape primer redesign or the need to add additional primers, as pathogen genetics tend to change in response to pressures such as antimicrobial use and laboratory testing strategies. The results listed here summarize impacts from pathogen genetics reported up to July 2011.

We acknowledge that other sentinel publications exist, and it is not the intent of the A6 process to limit their value to the microbiology community. However, due to the structure of the question being addressed and of the process structure, several key publications were omitted from analysis but are listed here for the reader (74–78).

While the LMBP process does not make quality judgments based on statistical power or statistical significance, the process does make quality judgments on whether the data used in the study are likely to be representative of the “true” impact of the practice. Many attributes, for example, quality of measurement, the measures used, the span of measurement, and the inclusion/exclusion criteria used in obtaining patients, can influence the representativeness of the results. If a study uses a census and a sufficiently long sampling period but still has few subjects, it is likely to get a good quality score for representativeness of the findings, regardless of the statistical properties of the finding. The effect size is graded separately from the quality of the study in order to produce that effect. There is also a very good paper by Ioannidis (79) worth citing to further describe this concept. The process is not intended to denigrate sentinel papers, nor will it do anything to stop sentinel papers from becoming sentinel papers or being referenced in reviews of the literature, as they should be. This LMBP review simply requires that certain criteria be met to be included in analysis. Definitions of the LMBP criteria are clearly defined and published so that if authors want to be included in the meta-analysis, they have clear guidelines to follow in future publications. In addition, Appendix 6 provides a toolkit or roadmap to assist authors in collecting all the information needed in order to provide data that can be included in a future meta-analysis.

Finally, this work represents not only the results of a meta-analysis, it represents the very first rigorous and programmatic systematic review collaboration among practicing clinical microbiologists, physicians, allied health care personnel, epidemiologists, and biostatisticians aimed to address key questions and con-

troversies in the practice of clinical microbiology. As with any “first,” there are limitations, some of which remain to be uncovered. It is the intent of the A6 process to continually uncover and disclose limitations with full transparency. Anyone can obtain raw data used for this evaluation from the American Society for Microbiology, and updates will be ongoing, as described in “Data Since the Time of Initial Review” below.

DATA SINCE THE TIME OF INITIAL REVIEW

While we acknowledge that there have been significant technological leaps since the inception of our work, based on the structure of the LMBP process, the new publications cannot contribute to the current document. We reference key publications that support or refute our conclusions and document the fact that these publications will be included in the next systematic review (74–78).

It was not our intent to review assay accuracy data; therefore, many publications, including many citing SeptiFast methods and matrix-assisted laser desorption ionization–time of flight (MALDI-TOF), were excluded because no outcome data relevant to the questions were reported in those papers relevant to the PICO question (1). The LMBP forces standardization of outcome and data points, such that the LMBP meta-analysis does indeed assess defined standard practice and data elements to which all the publications must comply to be included. Few manuscripts meet criteria to make it through the LMBP process; therefore, the process limits the inclusion of many articles. It is the intent of the CDC and ASM to promote transparent publications and data that are more easily comparable with systematic review statistics.

CONCLUSIONS AND RECOMMENDATION

On the basis of low overall strength of evidence of effectiveness, no recommendation is made for or against the use of the three assessed practices of this review due to insufficient evidence; however, the overall strength of evidence is simply classified as suggestive due to the fact that most studies received a fair study quality rating. Despite there being no firm recommendation, the data do suggest that each of these three practices has the potential to improve times to initiate targeted therapy and possibly improve other patient outcomes.

The findings of effectiveness are based on three published and two unpublished studies for rapid molecular techniques without additional direct communication, four published and three unpublished studies on rapid molecular techniques with additional direct communication, and four published studies on rapid phenotypic techniques with additional direct communication. A number of the unpublished studies have since been published and are listed in the references. Of the 16 included studies, 2 were rated to be of poor quality and thus not used to determine recommendations; only 3 were rated as being of good quality for estimating the results most relevant to the review question, and 11 were rated as fair. Of the 14 studies of fair or good quality, most, 10 total, were judged to have substantial effect sizes for improving outcomes, while 3 were judged to have a moderate effect size, and 1 had an effect size ranked as minimal to none. For both practices involving rapid molecular techniques, the low strength of evidence is based on inconsistent findings (attributable to one study) and the overall lack of studies determined to be of good quality. Though the evidence was consistent for the practice of

using phenotypic techniques with additional direct communication in improving outcomes, none of the four studies were rated as being of good quality and did not provide sufficient evidence supporting this practice.

The average standard difference in means for the three practices was as follows: -0.396 (95% CI, -0.888 to 0.44 ; not significant) for rapid molecular techniques; -1.483 (95% CI, -2.691 to -0.275 ; $P < 0.05$) for rapid molecular techniques, with additional direct communication; and -0.175 (95% CI, -0.279 to -0.072 ; $P < 0.05$) for phenotypic techniques, with additional direct communication. Standard differences in means less than zero favor the rapid test practice over the comparator practice. The meta-analysis results suggest that the implementation of any of the three practices may be more effective at increasing timeliness to targeted therapy than routine microbiology techniques for identification of the microorganisms causing BSIs. Based on the included studies, results for all three practices appear applicable across multiple microorganisms, including MRSA, *S. aureus*, *Candida* species, and *Enterococcus* species.

In conclusion, this article is a systematic review of the effectiveness of three rapid diagnostic practices for improving the timeliness of targeted therapy in patients with bloodstream infections (BSIs): rapid molecular techniques without additional direct communication, rapid molecular techniques with additional direct communication, and rapid phenotypic techniques with additional direct communication. The CDC-funded Laboratory Medicine Best Practices initiative systematic review methods for quality improvement practices were used. Fourteen studies met review inclusion criteria. Three were rated as being of good quality, and 11 were rated as fair. Most studies had substantial effect size ratings. The average standard difference in means for the three practices compared to more routinely performed practices favored the rapid test practice. However, because most studies were of only fair quality, the overall strength of evidence of effectiveness is only suggestive for each of the three practices in improving timeliness for targeted therapy in patients hospitalized with BSIs. Therefore, we are unable to make a recommendation for or against the three practices evaluated due to insufficient evidence. To create a more robust evidence base, a suggested roadmap for future studies is provided for use in preparing existing data or performing a prospective study for submission and effectiveness analysis for these practices (see Appendix 6).

APPENDIX 1

Elements Needed for Studies That Address This Systematic Review Question

1. General design. The study should be a pretest/posttest cohort study in defined hospital settings (i.e., large and small institutions) enrolling consecutive hospital inpatients suspected of having bloodstream infections (BSIs).
2. Sample size. The study sample should be sized according to the most relevant proximal outcome measure, i.e., the time to targeted therapy after conventional microbial identification techniques. We recommend that the study should be sized to detect $\geq 25\%$ reduction in the time to targeted therapy, with a 95% CI. If possible, demographic information, such as those listed in the Standards for Reporting of Diagnostic Accuracy (STARD) recommendations (80), should be included to de-

scribe the patient population, including age, gender, description of hospital ward stratification, etc. (see Appendix 3). Diagnosis-related group information for the patients should be included as well. Microbial prevalence during intervention periods should also be reported, if available.

3. Practice (intervention) and comparator. Practices of interest include rapid molecular techniques and/or a variety of phenotypic techniques. As part of the practice, rapid and direct communication of results from these techniques to pharmacists or physicians is also of interest. Both pretest and posttest practices should be equally well articulated and recognizable from their descriptions. Information on how reporting and recording practices are performed should also be described.
4. Outcomes. Proximal, patient-centered outcome measures should include, for each patient, the time from the detection of the patient's BSI to the time that the patient was placed on targeted therapy, as well as the time required to report the identification of the microbe causing the BSI. Length of stay and mortality should also be measured. If possible, time points to be recorded include the following:
 - a. the times that the BSI was detected and Gram stain results were reported to a clinician,
 - b. the time that the patient was placed on initial therapy,
 - c. the time that the identification and/or drug susceptibility test result was reported from the laboratory,
 - d. the time that targeted therapy was confirmed or the patient was switched to targeted therapy, and
 - e. the time that the pharmacist confirmed that the patient was on targeted therapy or the laboratory made a call to the clinician or infectious disease physician.
5. Analysis. Data analysis should include calculation of statistical significance of differences between the effects of the practice and comparator methods on the measured outcomes. Data averages (means) and standard deviations should be provided along with confidence intervals for all continuous data (e.g., time measures, including length of stay), while dichotomous measures (e.g., mortality) should include both the numerator (deaths) and denominator for both the pretest and posttest cohorts. These values will allow results to be included in the meta-analysis. If analyses linking rapid testing to distal morbidity and mortality outcomes are done, presentation upon admission and other patient characteristics and characteristics of their treatment should be statistically controlled in the analysis. Statistical assistance may be required to perform calculations.
6. Cost information. Cost information estimating all resources required for implementing and maintaining the intervention (new practice[s] of interest) and comparison practices, including, when appropriate, quantities and estimated unit costs and cost-related impacts, including savings, with supporting details associated with effectiveness outcomes are desired. Cost information observations should indicate the corresponding year and include reports concerning the following.
 - a. What planning costs were incurred in preparing for the new testing technology and over what time period?
 - b. What costs were incurred for purchasing new equipment, supplies, and software?
 - c. What training costs, if any, were associated with instituting the new testing technology?
 - d. What operational costs have been observed, and how do

these observed costs compare with those of the alternative practice(s)?

- e. What operational and patient care-related savings have been observed?
 - f. What additional financial consequences has your facility experienced as a result of instituting the new testing technology?
 - g. Were costs normalized or adjusted to include the health care consumer price index?
7. Additional considerations. Additional observations about implementing the practice that are of interest include reports concerning the following.
- a. What training was required to institute the new testing technology?
 - b. What systems modifications, if any, were required to accommodate implementation of the new practice?
 - c. Provide detailed information on how batching of samples was handled and what staff hours and availability were for implementing both the practice and comparator techniques.

APPENDIX 2

Glossary

additional direct communication An intervention communication by an infectious disease physician, pharmacist, or laboratory liaison recommending patient antimicrobial changes to the treating physician (51).

antimicrobial susceptibility testing An *in vitro* laboratory test used to determine if an antimicrobial agent will be active in killing or inhibiting the growth of a specific microorganism (32).

batch testing Laboratory tests performed based on designated time frames or when a specific number of tests has accumulated. This practice is chosen to save laboratory resources and reduce the cost per test (43).

bias Systematic error, threats to validity, a tendency to produce results that depart systematically from the “true” results. Unbiased results are internally valid. There are many kinds of bias. Four common types of bias are selection/allocation, performance, measurement/detection, and attrition/exclusion.

blood culture A set of two or more bottles of liquid culture medium into which a single blood specimen (typically 16 to 30 ml) is inoculated to detect the presence of bacteria in the blood. Normally, two bottles (one to two aerobic bottles and one anaerobic bottle or two aerobic bottles only) are inoculated for adults and one bottle for children (19, 32).

bloodstream infection An infection associated with bacteremia or fungemia (32).

broad-spectrum antibiotic An antibiotic that has the capacity to kill or inhibit two or more types of bacteria (19).

consensus All eligible patients within a specified time period.

consistency The degree to which estimates of effects (specific outcomes) are similar across the included studies.

continuous-monitoring blood culture systems Laboratory instruments into which blood culture bottles containing the patient’s blood are placed and monitored over the course of 24 h for 5 to 7 days in order to detect increased CO₂ production or to measure gas pressure in the headspace of the culture bottle when microbial growth occurs (19, 32).

critical value The first laboratory result (e.g., Gram stain or another rapid test) which is communicated verbally and/or electronically to a licensed health care provider as soon as possible (within 60 min) after laboratory verification of the abnormal result (19, 32). See the definition for “direct communication.”

direct communication Active transfer of laboratory test results (of crit-

ical value) to a licensed caregiver by telephone or other direct electronic method rather than passive communication of information into the laboratory information system. Initial blood culture test results are routinely reported to a clinician’s staff by the laboratory for the particular patient as soon as they are available.

d-score Standardized difference in means where the mean from one group (\bar{X}_{G2}) is subtracted from the mean from the second group (\bar{X}_{G1}) and the result is divided by the pooled standard deviations of the means (S_p). The *d*-score represents a position on a *z*-distribution.

$$ES_{sm} = \frac{\bar{X}_{G1} - \bar{X}_{G2}}{S_p}$$

effect size A value which reflects the magnitude of the difference between a study’s outcome measures for the group in which the intervention/practice was evaluated and those of its control or comparison group.

empirical therapy Initiation of broad-spectrum treatment before a firm diagnosis or etiology is determined (43).

external validity, generalizability, applicability Extent to which the effects observed in the study are applicable to other populations and settings outside the study.

false negative A culture bottle set that may not grow a microorganism for a few possible reasons, namely, (i) the infecting organism is not supported by the culture medium, (ii) the organism cannot be grown in culture and requires serological or molecular amplification, or (iii) the organism is inhibited by the presence of antimicrobial agents or human immune factors present in the blood prior to collection of the culture sample (19).

false positive A blood culture contaminated with one or more organisms, typically skin flora. False-positive blood cultures are commonly contaminated with organisms introduced from the skin during specimen collection, typically coagulase-negative staphylococci, viridans group streptococci, corynebacteria, *Propionibacterium* spp., or *Bacillus* spp., not *Bacillus anthracis*. It is very important to rapidly determine whether Gram-positive cocci observed in clusters are coagulase-negative staphylococci or *S. aureus* and to further confirm whether the *S. aureus* is methicillin resistant (19).

fungemia The presence of fungi (yeasts or molds) in the bloodstream (19, 32).

Gram stain A differential stain used primarily to separate bacteria into two large groups (Gram positive and Gram negative) based on the physical properties of their cell walls. Bacteria can further be distinguished visually based on their shape, size, and arrangement. Gram stain characteristics may be used to classify bacteria into genera and determine or assist in switching from empirical to a more targeted therapy until more specific genus/species identification and susceptibility test results are available (43).

I² A statistic related to *Q* which quantifies the proportion of total variability owing to heterogeneity. *I*² is a standardized statistic, generally stated as a percentage between 0% and 100%.

internal validity Extent to which the design and conduct of the study are likely to prevent systematic error. Internal validity is a prerequisite for external validity.

meta-analysis The process of using statistical methods to standardize and quantitatively combine the results of similar studies in an attempt to allow inferences to be made from the sample of studies and be applied to the population of interest.

MicroScan system (Siemens) An automated phenotypic bacterial identification and drug susceptibility testing system. The system has two types of testing formats: one for conventional overnight testing and another for rapid testing (63).

molecular test A diagnostic test that analyzes the presence or expression of genes or smaller genetic targets, DNA mutations, or RNA sequences. Examples of molecular tests are PCR and PNA-FISH.

odds ratio (OR) The ratio of the odds of an event in one group to the odds

of an event in another group. One group is the treatment or intervention group and the other group is the control or usual-practice group. The odds in the treatment group are usually divided by the odds in the control or usual-practice group. An OR of 1 means the two practices are equally successful (no difference in reducing risk with respect to the outcome evaluated); an OR of >1 means the treatment or intervention practice is more successful; and an OR of <1 means the treatment or intervention practice is less successful. When the risk is small, odds ratios are very similar to risk ratios.

PCR A molecular technique which amplifies a small amount of a microorganism DNA by logarithmic magnitudes so that it can be detected for diagnosis of pathogens and drug resistance (36, 37).

peptide nucleic acid fluorescent *in situ* hybridization (PNA-FISH) probes DNA mimics with a noncharged peptide backbone. This allows the probes to target individual-species-specific targets on the 16S rRNA within bacteria or the 18S rRNA within fungi (54).

phenotypic test Nonmolecular tests which measure activities such as enzymes or the presence of certain antigens, etc. (36, 37).

Q By convention, a statistic which measures heterogeneity. The traditional *Q* is Cochran's *Q*, which is a dimensional extension of McNemar's test, the latter being a test for homogeneity in 2-by-2 tables. In the meta-analysis arena, *Q* tests for heterogeneity across some set of *n* different. A shortcoming of Cochran's *Q* is its poor performance when *n* is small, which is frequently the case in meta-analysis. In response to this weakness, another *Q* statistic—Cohen's *q*, or Cohen's *Q*—has been defined by the statistical community and applied commonly in meta-analysis. It is a measure of heterogeneity which relies on correlations between the studies. Cochran's *Q* has a χ^2 distribution. Cohen's *q* is standard normal.

rapid diagnostic technique A microorganism identification or susceptibility test performed within the time frame of <6 to 8 h (although some tests are performed in time frames of 2 to 3 h), as defined by agreement of the BSI expert panel (see Appendix 3).

septicemia A serious systemic illness caused by microorganisms and microbial toxins circulating in the bloodstream (52).

standardized Transformed to a common metric allowing direct comparison of data across studies.

standardized difference in means (*d*-score) Difference in pretest and posttest means divided by the pooled standard deviation (see entry for *d*-score).

systematic review A scientific investigation that focuses on a specific question and that uses explicit, planned scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may or may not include a quantitative synthesis of the results from separate studies (meta-analysis).

targeted therapy Antimicrobial treatment directed specifically to a microorganism based on the genus and species of that organism or actual susceptibility test results (30).

turnaround time (TAT) The time that it takes to perform and report a laboratory test result from the time that the sample is received in the laboratory.

transparency Methods are explicitly defined, consistently applied, and available for public review so that observers can readily link judgments, decisions, or actions to the data on which they are based. Transparency allows users to assess the strengths and weaknesses of the systematic review and to provide associated guidance and recommendations.

Vitek system (bioMérieux) An automated antimicrobial system used for performing identification and drug susceptibility testing on microorganisms. The Vitek system uses a number of different card-based bacterium, yeast, and antibiotic susceptibility panels. The Vitek 1 system is for 18- to 24-h testing, while the Vitek 2 system can be used for 18- to 24-h testing as well as for rapid identification, for which results are generally completed within 6 to 8 h (36, 37).

weighted difference in means The difference between two means weighted by the precision of the study.

without additional direct communication The standard practice of communicating a critical value (an initial positive result) for a positive blood culture laboratory test result to a licensed caregiver, and when an additional rapid test result and/or culture result is available, the blood culture report is updated in the computer without direct communication to the caregiver.

APPENDIX 3

LMBP Bloodstream Infection Expert Panel Members

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APPENDIX 4

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APPENDIX 5

Evidence Summary Tables for Rapid Molecular Techniques with No Additional Direct Communication Practice

Consult [Tables A1 to A7](#) for evidence summary tables for rapid molecular techniques with no additional direct communication. For scoring information, see Christenson et al. (1). Boldface results were used for analysis. Papers with outcome measures of interest (but not those outcomes considered relevant for analysis purposes) are also included. No effect rating or relevance is provided for those studies.

TABLE A1 Evidence summary table and scoring criteria for reference 52^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
Authors: Allaouchiche et al. (52) Yr: 1999 Publication: J Infect Affiliations: Intensive Care Unit, Hotel Dieu Hospital, Lyon, France; Department of Microbiology, Edouard Herriot Hospital, Lyon, France Funding: none noted	Design: randomized controlled study; patients were randomly assigned to rapid PCR or traditional overnight testing for susceptibility; all patients were initially treated with vancomycin, except 54 who were determined to have no <i>mecA</i> gene by PCR; antibiotic treatment was modified at receipt of susceptibility results Facility/setting: not provided Time period: 3 yr Populations/samples: PCR group, 72 patients; traditional-test group, 73 patents; all were inpatients and had nosocomial <i>S. aureus</i> bacteremia; there was no statistically significant difference between the groups Comparator: traditional overnight techniques, i.e., tests for clumping factor, coagulase, heat-stable DNase, biochemical characters, and MIC Study bias: single center; serial samples within cases	Description: multiplex PCR assay Duration: 3 yr Training: none described Staff/other resources: none described; PCR-related equipment and assays were required Cost: none provided	Description: (i) Mortality (ii) LOS in ICU (iii) Cost of antibiotics Recording method: (i) for mortality, death during hospitalization in the ICU; (ii, iii) for LOS and cost of antibiotics, not discussed	Types of findings: comparisons Findings/effect size for control vs PCR: (i) Mortality: 16.43% (12/73) vs 20.83% (15/72); 95% CI for the difference, -17.35–8.50% ($P =$ 0.497) (ii) LOS (days): 18 (SD, 2) ($n = 54$) + 21 (SD, 3) ($n = 18$) vs 17 (SD, 3) ($n = 46$) + 26 (SD, 2) ($n = 27$) (iii) Cost of antibiotics: \$2,105 (SD, \$303) ($n = 54$) + \$6,264 (SD, \$836) ($n = 18$) vs \$1,882 (SD, \$290) ($n = 46$) + \$4,816 (SD, \$994) ($n = 27$) Statistical significance/tests: Authors assumed an <i>a priori</i> 90% success rate of patients tested by PCR; thus, at least 2 groups of 43 patients had to be included to detect a difference of $\geq 25\%$ with a power of 80% and a one-sided α level of 0.05; Student's <i>t</i> test for quantitative data; Fisher's exact test or χ^2 test, with $P < 0.05$ Results/conclusion biases: none
Quality rating: 5 (poor) (10-point maximum) Effect size magnitude rating: NA (less-direct relevance)	Study (3-point maximum): 1 (facility not sufficiently described; study bias, generalizability of old therapies to current practices)	Practice (2-point maximum): 1 (reporting of results not well described)	Outcome measures (2-point maximum): 2	Results/findings (3-point maximum): 1 (uncontrolled bias)

^a Roman numerals within and between columns refer to the descriptions under "Outcome measures." NA, not applicable.

TABLE A2 Evidence summary table and scoring criteria for Frye et al., unpublished (now published as reference 51)^a

Bibliographic information	Study description	Practices	Outcome measures	Results/findings
<p>Authors: Frye et al., unpublished Yr: unpublished Publication: NA Affiliations: Department of Pharmacy, Providence St. Vincent Medical Center; Center for Outcomes Research and Education; Department of Laboratory Services and Department of Medical Education, Providence Portland Medical Center; and Department of Medicine, Oregon Health and Science University, Portland, OR Funding: none</p>	<p>Design: retrospective interventional cohort; pretest vs posttest Facility/setting: two 500-bed tertiary-care medical centers Time period: pretest, 15 Jan 2009–14 Jan 2010; posttest, 15 Jan 2010–14 Jan 2011 Populations/samples: pretest group $n = 68$ (<i>S. aureus</i>) and 66 (CoNS), posttest group $n = 58$ (<i>S. aureus</i>) and 52 (CoNS); inpatients with blood cultures positive for GPC; >18 yr old; some exclusions; no statistics for significant differences between groups Comparator: Gram stains of all positive BCs called to the patient's floor or physician's office within 60 min; typical colony morphology, Gram-positive cocci, positive catalase test and positive latex coagulase test; PBP2a latex agglutination test for MRSA and MSSA differentiation; MRSA ID called to patient's floor, all other results released to the EMR Study bias: none</p>	<p>Description: PCR; real-time Becton, Dickinson GeneOhm Staph single-reaction PCR assay; post-PCR implementation, laboratory services completed batched PCR; non-MRSA results were reported to the EMR without additional intervention; Gram stains of all positive BCs called to the patient's floor or physician's office within 60 min of the BC bottle turning positive; PCR runs were batched twice daily Monday to Friday and once daily on weekends; PCR results released to the EMR; PCR MRSA results called to the floor; clinician notification same as for pretest group Duration: 1 yr Training: clinicians were educated about new PCR process via the lab's regular notification process Staff/other resources: none provided Cost: none provided</p>	<p>Description: (i) LOS (ii) Mortality (iii) Time to report an ID (iv) Time to targeted therapy (v) Reduction in broad-spectrum antibiotic use Recording methods: data were extracted from the EMR; a diagnostic work-up was extracted from the laboratory information system; T_0 was defined as the time that the BC specimen was collected; optimal, suboptimal, and nonoptimal antibiotic therapy was defined based on the species isolated and the organism's susceptibility to methicillin; (iii) for the times to report an ID, the T_0 was the mean time (range) until reporting to the EMR; (iv) for the time to targeted therapy, the times from a positive BC to the start of or switch to optimal antibiotics were reported as means (ranges); (v) for reductions in broad-spectrum antibiotic use, the impact of PCR implementation on suboptimal vancomycin use was considered; the no. of hours between a positive result and the start of optimal therapy or discontinuation of unnecessary vancomycin were reported as means (ranges)</p>	<p>Types of findings: pretest vs posttest Findings/effect size: (i) Pretest LOS = 12.1 days, posttest LOS = 11.6 days ($P > 0.1$) (ii) Pretest mortality = 12.7% (17/134), posttest mortality = 12.7% (14/110) ($P > 0.1$) (iii) The mean overall times to report an ID (range) were 47.3 h (24.5–77.4 h) for the pretest group ($n = 129$) and 34.1 h (16.9–66.0 h) for the posttest group ($n = 106$); the difference (95% CI) was 13.2 h (10.2–15.9 h) ($P < 0.0001$) The times to report MRSA were 42.0 h (26.4–70.1 h) in the pretest group ($n = 24$) vs 30.6 h (22.4–55.3 h) for the posttest group ($n = 23$); the difference (95% CI) was 11.4 h (5.2–17.5 h) ($P = 0.0004$) The times to report MSSA were 44.6 h (24.5–70.5 h) for the pretest group ($n = 44$) vs 28.0 h (16.9–47.2 h) for the posttest group ($n = 33$); the difference (95% CI) was 16.6 h (12.2–21.0 h) ($P < 0.0001$) The times to report CoNS were 53.3 h (30.4–85.4 h) for the pretest group ($n = 65$) vs 40.5 h (20.1–82.5 h) for the posttest group ($n = 51$); the difference (95% CI) was 12.8 h (8.0–17.4 h) ($P < 0.0001$) (iv) The mean (range) times to target therapy for <i>S. aureus</i> were 23.8 h (0.2–74.7 h) for the pretest group ($n = 61$) vs 25.0 h (0.5–91.3 h) for the posttest group ($n = 55$); the difference (95% CI) was 1.2 h (–5.1, 9.8 h) ($P > 0.1$) The mean (range) times to target therapy for MRSA were 10.7 h (0.22–24.72 h) for the pretest group ($n = 22$) vs 14.4 h (0.67–36.88 h) for the posttest group ($n = 24$); the difference (95% CI) was 3.7 h (–1.8, 9.1 h) ($P > 0.1$) The mean (range) times to target therapy for MSSA were 32.8 h (0.27–96.1 h) for the pretest group ($n = 40$) vs 35.1 h (0.52–98.48 h) for the posttest group ($n = 32$); the difference (95% CI) was 2.3 h (–10.5, 15.2 h) ($P > 0.1$) (v) The mean (range) durations of suboptimal vancomycin therapy for MSSA were 46.8 h (17.1–87.1 h) for the pretest group ($n = 37$) vs 38.1 h (10.7–82.1 h) for the posttest group ($n = 25$); the difference (95% CI) was –8.7 h (–19.0, 1.5 h) ($P = 0.09$) The durations of unnecessary vancomycin therapy for CoNS were 35.4 h (14.8–67.7 h) for the pretest group ($n = 23$) vs 34.3 h (11.1–58.6 h) for the posttest group ($n = 21$); the difference (95% CI) was –1.1 h (–10.7, 7.8 h) ($P > 0.1$) The times to discontinuation of antibiotics for clinically insignificant CoNS were 60.2 h (32.8–89.6 h) for the pretest group ($n = 23$) vs 57.4 h (35.5–87.0 h) for the posttest group ($n = 23$); the difference (95% CI) was –2.8 h (–11.1, 5.5 h) ($P > 0.1$) Statistical significance/tests: Student t tests or ANOVA was used to compare differences in means; the 2-sided type I error rate was 5%; cases falling more than 1.5 times the IQ range outside the 1st or 3rd quartile of the sample distribution were omitted; t tests of mean LOSs were performed on the log transformation of the no. of days; mean times were compared first with ANOVA controlling for confounders; if confounding effects were found, ANOVA was used in the final analysis of the means; otherwise, t tests were used Results/conclusion biases: small sample size</p>
<p>Quality rating: 9 (good) (10-point maximum) Effect size magnitude rating: minimal/none (direct relevance)</p>	<p>Study (3-point maximum): 3</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 2 (recording method not well described)</p>	<p>Results/findings (3-point maximum): 2 (small sample size)</p>

^a EMR, electronic medical records; T_0 , time zero; ANOVA, analysis of variance; IQ, interquartile range.

TABLE A3 Evidence summary table and scoring criteria for reference 48

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Hallin et al. (48) Yr: 2003 Publication: J Clin Microbiol Affiliations: Laboratory of Microbiology and Infectious Diseases Clinic, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium Funding: not provided</p>	<p>Design: prospective cohort group; comparator and practice tests were performed on the same samples Facility/setting: none provided; infectious disease specialists evaluated the implementation or adaptation of treatment Time period: 8 mo Populations/samples: 35 adult inpatients suspected of having staphylococcal BSIs (some exclusions) Comparator: 24-h subculture on Columbia agar with 5% sheep blood, a coagulase test in human plasma, and an agglutination test with a Pastorex Staph Plus kit; disk diffusion; the rapid ATB-Staph microdilution test; a call was made to the clinician in charge of the patient upon Gram staining and conventional test results Study bias: case within control design</p>	<p>Description: PCR; call made to the clinician in charge of the patient by a microbiologist with PCR results; the PCR method is labor-intensive and relatively expensive, does not discriminate mixed cultures, and neither provides a complete susceptibility profile nor identifies CoNS to the species level Duration: 8 mo Training: none noted Staff/other resources: infectious disease specialists who evaluated the implementation or adaptation of treatment; microbiologist; other supplies not detailed Cost: \$30/assay, including material and labor</p>	<p>Description: (i) Time to results communication (time to report ID) Recording method: (i) the turnaround time to result communication was the time elapsed between reporting of the Gram stain result and notification of either PCR or conventional method results</p>	<p>Types of findings: comparative Findings/effect size: (i) For PCR, the mean turnaround time was 6 h 8 min (range, 4 h 50 min–7 h 30 min), whereas the conventional methods took a mean time of 36 h 39 min (range, 27 h 35 min–51 h 1 min) for <i>S. aureus</i> and 49 h 16 min (range, 47 h 6 min–51 h 21 min) for CoNS. Thus, PCR provided results on avg 39 h earlier than conventional methods ($P < 0.01$) Statistical significance/tests: not described Results/conclusion biases: small sample size</p>
<p>Quality rating: 6 (fair) (10-point maximum) Effect size magnitude rating: substantial (direct relevance)</p>	<p>Study (3-point maximum): 1 (facility not described; located in Europe, where infectious disease specialist was needed; case within control design)</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 1 (sample size likely too small for robust estimate of practice)</p>

TABLE A4 Evidence summary table and scoring criteria for reference 53

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Holtzman et al. (53) Yr: 2011 Publication: J Clin Microbiol Affiliations: Department of Pharmacy, Boston Medical Center; Section of Infectious Diseases, Department of Medicine, and Department of Pathology and Laboratory Medicine, Boston Medical Center; and Boston University School of Medicine, Boston, MA Funding: Department of Pathology and Laboratory Medicine at Boston Medical Center for Biostatistics Services</p>	<p>Design: retrospective pretest vs posttest study Facility/setting: Boston Medical Center Time period: pretest, May 2005–Oct 2006; posttest, Dec 2006–May 2008 Populations/samples: pretest group, $n = 100$; posttest group, $n = 99$; used random-no. generator to find patients with BCs positive for CoNS in defined time periods; no statistically significant difference between groups Comparator: typical laboratory practices; positive Gram stain critical action value verbally communicated (within 60 min) to a relevant licensed care provider and documented in the EMR Study bias: none noted</p>	<p>Description: PNA-FISH; blood culture reports were updated with PNA-FISH results in the EMR by 5 a.m. the following morning, but verbal notification was not repeated Duration: 18 mo Training: not noted Staff/other resources: not noted Cost: not provided</p>	<p>Description: (i) LOS (ii) Time to broad-spectrum antibiotic use Recording method: For CoNS bacteria, an electronic medical record was used to collect all information; (i) the LOS was the no. of days before and after the introduction of the PNA-FISH assay; the mean LOS ratio was the ratio of the mean LOS for the pre-PNA-FISH group to the mean LOS for the post-PNA-FISH group. For the time to broad-spectrum antibiotic use, (ii) the no. of days of vancomycin treatment as a response to a positive Gram stain from a signal-positive blood culture was used</p>	<p>Types of findings: pretest vs posttest Findings/effect size: (i) The mean hospital LOS was the mean (SD) (median; range) no. of days. For the pretest group, the LOS was 18.7 (SD, 16.5) (13.0; 2.0–83.3) days vs 20.9 (SD, 21.0) (13.7; 1.8–113.5) days for the posttest group ($P = 0.35$) The mean LOS ratio was 0.89 (95% CI, 0.70–1.13) (ii) The no. of days of vancomycin treatment was reported as the mean (SD) (median; range). For the pretest group, it was 4.15 (SD, 4.03) (2.9; 0.3–19.2) days vs 3.51 (SD, 3.43) (1.8; 0.3–10.8) days for the posttest group ($P = 0.49$) Statistical significance/tests: 80% power to detect difference in LOSs of 1.5 days with a sample size of 100 patients per group; Student's t test for differences in vancomycin durations; multivariable gamma regression with a log link function for LOS analysis Results/conclusion biases: none noted</p>
<p>Quality rating: 5 (poor) (10-point maximum) Effect size magnitude rating: NA (relevance NA)</p>	<p>Study (3-point maximum): 1 (excluded with increased LOS; CoNS excluded; time periods far apart and no adjustments for morbidity differences)</p>	<p>Practice (2-point maximum): 1 (care provider not well described)</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 1 (uncontrolled bias)</p>

TABLE A5 Evidence summary table and scoring criteria for reference 49

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Nguyen et al. (49) Yr: 2010 Publication: J Clin Microbiol Affiliations: Department of Pathology and Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, CA; Clinical Microbiology Laboratory and Department of Pharmacy, Stanford Hospital and Clinics, Palo Alto, CA; and Department of Pharmacy, Lucile Packard Children's Hospital, Palo Alto, CA Funding: none</p>	<p>Design: pretest vs posttest Facility/setting: Stanford Hospital (large academic hospital) Time periods: Pretest, Dec 2007–May 2008; posttest, Dec 2008–May 2009 Populations/samples: pre-PCR = 65 samples, post-PCR = 94 samples; adult inpatients receiving empirical vancomycin therapy at the time that positive cultures for methicillin-susceptible staphylococcus were reported Comparator: phenotypic testing with MicroScan Walkaway test; methicillin resistance upon overnight growth on oxacillin-containing agar Study bias: none noted</p>	<p>Description: PCR; <i>mecA</i> real-time PCR; delivery of results was by the standard hospital information system interface Duration: 6 mo Training: none noted Staff/other resources: none noted Cost: not provided</p>	<p>Description: (i) Vancomycin usage (broad-spectrum antibiotic use) (ii) LOS (iii) Time to antibiotic replacement (time to targeted therapy) Recording method: electronic laboratory and pharmacy reports with combined databases; (i) for vancomycin usage, the no. of days from the time that a positive culture ID was reported by the hospital information system to the time of vancomycin termination; (ii) For LOS, the no. of days of hospitalization from the time that positive cultures were reported; EMR technicians reviewed reports for the date of discharge</p>	<p>Types of findings: pretest vs posttest Findings/effect size: (i) For vancomycin usage, pre-PCR = median of 3 days (range, 1–44 days) vs post-PCR = median 1 day (range, 0–18 days) ($P < 0.0001$) Vancomycin therapy was replaced with targeted therapy in 47.7% (31/65) of pretest patients vs 73.4% (69/94) of posttest patients (ii) For LOS, the median was 8 days for pretest patients (range, 1–47 days) vs 5 days (range, 0–42 days) for posttest patients ($P = 0.03$) (iii) The median time to vancomycin replacement (time to targeted therapy) was 5 (range, 1–45) days in the pre-PCR group vs 2 (range, 1–18) days in the post-PCR group ($P < 0.0001$) Statistical significance/tests: (i) For vancomycin usage, Wilcoxon's test for medians and the χ^2 test for proportions; (ii) For LOS, ANOVA with adjustments (iii) For the median time to antibiotic replacement, Kaplan-Meier curve analysis Results/conclusion biases: small sample size</p>
<p>Quality rating: 9 (good) (10-point maximum) Effect size magnitude rating: substantial (direct relevance)</p>	<p>Study (3-point maximum): 3</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 2 (sample size may not be sufficient to allow robust estimate of results)</p>

TABLE A6 Evidence summary table and scoring criteria for reference 50

Bibliographic information	Study ^a	Practice	Outcome measures	Results/findings
<p>Authors: Parta et al. (50) Yr: 2010 Publication: Infect Control Hosp Epidemiol Affiliations: Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX Funding: Cepheid provided materials used in the study</p>	<p>Design: pretest vs posttest Facility/setting: Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX Time period: group 1 (posttest) 4 Jan–15 July 2009; group 2 (pretest) 1 Jan–31 Dec 2008 Populations/samples: posttest group $n = 58$ (the doctor was notified of positive BCs from PCR); pretest group $n = 106$ (BC yielded Gram-positive cocci) (1 Jun–31 Dec 2008) and MSSA (1 Jan–31 May 2008) by the comparator method; patients with BCs presumed to be staphylococci (some exclusions) Comparator: traditional microbiologic laboratory techniques; group 2 doctors were notified of positive BC results immediately after Gram staining; follow-up was 48–72 h later with identification to the species level Study bias: the ratio of <i>Staphylococcus</i> species other than <i>S. aureus</i> to <i>S. aureus</i> was greater than estimated; a disproportionate no. of group 1 patients received MRS drug for unrelated condition; relied on statements in doctors' progress notes</p>	<p>Description: PCR; Cepheid Xpert MRSA/MSSA; physician notified of results Duration: 6 mo Training: not provided Staff/other resources: not provided Cost: not provided</p>	<p>Description: (i) Time to initiate targeted therapy (ii) Duration/length of broad-spectrum therapy Recording method: medical records; physicians' notes; (i, ii) initiation or discontinuation was defined as the time at which an order was signed electronically by a doctor; the starting time for observations was the time that the doctor was notified of the BC result</p>	<p>Types of findings: pretest vs posttest Findings/effect size: (i) MSSA mean time to initiate targeted therapy: 5.2 h (group 1 [$n = 12$]) vs 49.8 h (group 2 [$n = 48$]) ($P = 0.007$); median time: 0 h (group 1 [$n = 12$]) vs 48.5 h (group 2 [$n = 48$]) ($P = 0.004$) For MRSA, mean time to initiate targeted therapy: 1.1 h (group 1 [$n = 8$]) vs 5.8 h (group 2 [$n = 50$]) ($P = 0.33$) (ii) For <i>Staphylococcus</i>, mean duration of broad-spectrum therapy: 31.8 h (group 1 [$n = 14$]) vs 44.0 h (group 2 [$n = 48$]) ($P = 0.03$) Patients treated for 0–168 h: 36% (5/14) of group 1 vs 65% (31/48) of group 2 ($P < 0.01$) Patients treated for >168 h: 64% (9/14) of group 1 vs 35% (17/48) of group 2 ($P = 0.42$) Statistical significance/tests: Wilcoxon-Mann-Whitney for means; K-sample test for medians; χ^2 test for proportions Results/conclusion biases: small sample size</p>
<p>Quality rating: 6 (fair) (10-point maximum) Effect size magnitude rating: substantial (direct relevance)</p>	<p>Study (3-point maximum): 2 (population was not well described and results are likely not generalizable; potential study bias [see above]; 1 yr for MRSA and 6 mo for <i>S. aureus</i>)</p>	<p>Practice (2-point maximum): 1 (notification of physician after PCR results was not well described or defined; done only on the day shift)</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 1 (sample size was likely too small to provide robust estimate of practice; data were collected during notably different time periods; high no. of non-<i>S. aureus</i> samples)</p>

^a MRS, multidrug-resistant *Staphylococcus*.

TABLE A7 Evidence summary table and scoring criteria for unpublished data contributed by listed authors

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: K. A. Stellrecht, M. L. Grifasi, E. M. Graffunder, and T. P. Lodise, unpublished</p> <p>Yr: unpublished; taken from 2009 ICAAC poster</p> <p>Publication: not applicable</p> <p>Affiliations: Albany Medical Center, Albany, NY, and Albany College of Pharmacy, Albany, NY</p> <p>Funding: none noted</p>	<p>Design: a retrospective, population-based, case-controlled study</p> <p>Facility/setting: Albany Medical Center, NY</p> <p>Time period: 1 Jan 2005–18 Apr 2007</p> <p>Populations/samples: 186 patients and controls with <i>S. aureus</i> BSIs as defined by CDC criteria; cases, $n = 136$ (with PCR detection of <i>S. aureus</i> BSI); controls, $n = 50$ (with <i>S. aureus</i> BSIs identified by standard culturing and susceptibility testing)</p> <p>Comparator: standard culturing and susceptibility testing; colony and Gram stain morphology along with catalase and coagulase reaction; Kirby-Bauer disk diffusion for susceptibility</p> <p>Study bias: none noted</p>	<p>Description: PCR</p> <p>Duration: 2 yr 3 mo</p> <p>Training: none noted</p> <p>Staff/other resources: none provided</p> <p>Cost: \$27.50/sample</p>	<p>Description:</p> <p>(i) LOS</p> <p>(ii) Time to treatment (targeted therapy)</p> <p>(iii) Broad-spectrum (vancomycin) antibiotic use</p> <p>(iv) Time to report identification</p> <p>Recording method: details not provided; (iv) the time to report an identification was from collection until the report of AST results</p>	<p>Types of findings: cases vs controls</p> <p>Findings/effect size:</p> <p>(i) Median LOS for MSSA: 23 days (comparator, $n = 25$) vs 14.5 days (PCR, $n = 64$) ($P = 0.10$)</p> <p>(ii) Median times to treatment of MRSA: 37 h 26 min (comparator, $n = 25$) vs 18 h 0 min (PCR, $n = 72$) ($P = 0.06$); median times to treatment of MSSA: 8 h 1 min (comparator, $n = 25$) vs 11 h 10 min (PCR, $n = 64$) ($P = 0.35$)</p> <p>(iii) Median no. of days for broad-spectrum treatment of MSSA: 2.5 days (comp, $n = 25$) vs 1 day (PCR, $n = 64$) ($P = 0.03$); median total no. of grams of vancomycin for MSSA: 4 g (comparator, $n = 25$) vs 2 g (PCR, $n = 64$) ($P = 0.03$)</p> <p>(iv) Median time to report identification of MRSA: 65 h 25 min (comparator, $n = 25$) vs 23 h 45 min (PCR, $n = 72$) ($P < 0.001$)</p> <p>Statistical significance/tests: continuous variables with Mann-Whitney U test; categorical variables with Pearson χ^2 test</p> <p>Results/conclusion biases: small sample size; more cases than controls</p>
<p>Quality rating: 6 (fair) (10-point maximum)</p> <p>Effect size magnitude rating: substantial (direct relevance)</p>	<p>Study (3-point maximum): 2 (facility not well described)</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 1</p> <p>Recording methods not well described</p>	<p>Results/findings (3-point maximum): 1 (sample size likely too small to allow for robust estimate of practice)</p>

Evidence Summary Tables for Rapid Molecular Techniques with Additional Direct Communication Practice

Tables A8 to A19 are evidence summary tables for rapid molecular techniques with additional direct communication. For scoring information, see Christenson et al. (1). Boldface results

were used for analysis. Papers with outcome measures of interest (but not those outcomes considered relevant for analysis purposes) are also included. No effect rating or relevance is provided for those studies.

TABLE A8 Summary table and scoring criteria for reference 55^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Bauer et al. (55) Yr: 2010 Publication: Clin Infect Dis Affiliations: Departments of Pharmacy and Pathology, The Ohio State University Medical Center Division of Infectious Diseases, College of Medicine, The Ohio State University Medical Center Funding: Supported by manufacturer (Cepheid)</p>	<p>Design: single-center study; pre/postimplementation; nonequivalent comparative study Facility/setting: Ohio State University Medical Center, a 1,150-bed tertiary-care facility in Columbus, OH Time period: pretest, 1 Sept 2008–31 Dec 2008; posttest, 10 Mar 2009–30 June 2009 Populations/samples: all adult inpatients with positive BC result for <i>S. aureus</i> bacteremia admitted during time period; pretest = 74 patients; posttest = 82 patients Comparator: MicroScan Walkaway Plus system and/or ceftioxin disk; lab notified doctor with Gram stain; final ID and susceptibility completed in 24–72 h and reported in the EMR without notification to doctor Study bias: infectious disease PharmD not available for notification 24/7; antimicrobial stewardship program may limit generalizability</p>	<p>Description: rPCR; rPCR result was paged to infectious disease PharmD Monday through Friday 8 a.m.–5 p.m. or logged by lab and reviewed by infectious disease PharmD on next business day; rPCR result was paged to doctor within 10 min; infectious disease PharmD paged the treating doctor, communicated the clinical interpretation of lab results, and recommended targeted therapy and an infectious disease consultation; pharmacist could enter verbal prescription order into computerized entry system Duration: 4 mo; 10 Mar 2009–30 June 2009 Training: none described Staff/other resources: rPCR performed 24/7 using Cepheid Xpert MRSA kit in conjunction with GeneXpert real-time PCR platform; OSUMC antimicrobial stewardship program includes infectious disease physician, 3 infectious disease Pharms, and research data manager Cost: \$35,000 for GeneXpert; \$65 for MRSA kit test</p>	<p>Description: (i) Time to antibiotic switch (time to targeted therapy) (ii) LOS (iii) Mortality (iv) Mean total hospital costs/patient (v) No. of patients in which PharmD initiated antibiotic changes (reduction in broad-spectrum antibiotic use) Recording method: (i) antibiotic switch = difference between dates of first dose of initial antibiotic and second antibiotic; (ii) LOS = difference between admission and discharge dates; (iv) mean total hospital cost was based on actual costs incurred by patients (obtained from OSUMC Information Warehouse); (v) no. of times PharmD switched patients from vancomycin was recorded</p>	<p>Types of findings: pretest/posttest; pretest ($n = 74$) vs posttest ($n = 82$) (unless otherwise noted below) Findings/effect size: (i) Time to antibiotic switch for MSSA, 3.6 days pretest vs 2 days posttest ($P = 0.002$); for MRSA, 10 days pretest vs 4.5 days posttest ($P = 0.15$) (ii) LOS pretest = 21.5 days (SD, 22.8 days) vs posttest = 15.3 days (SD, 14.1 days) ($P = 0.07$) (iii) Mortality in rPCR patients was not independently associated with hospital mortality (OR = 0.65, 95% CI, 0.3–1.39); pretest = 19 patients vs posttest = 15 patients ($P = 0.33$) (iv) Mean total hospital cost/patient pretest = \$69,737 (SD, \$96,050) vs posttest = \$48,350 (SD, \$55,196) ($P = 0.03$) (v) No. of MSSA patients for whom PharmD initiated an antibiotic change, pretest $n = 8$ patients vs posttest $n = 27$ patients ($P = 0.004$); for MRSA patients, pretest $n = 3$ patients vs posttest $n = 4$ patients ($P = 0.26$); pretest $n = 44$ patients vs posttest $n = 37$ patients with MRSA; pretest $n = 30$ patients, posttest $n = 45$ patients with MSSA Statistical significance/tests: χ^2 or Fisher's exact test for qualitative results; Student's t test or the Wilcoxon rank sum test for quantitative results; $P = 0.05$ Results/conclusion biases: none</p>
<p>Quality rating: 8 (good) (10-point maximum) Effect size magnitude rating: moderate (direct relevance)</p>	<p>Study (3-point maximum): 2 (infectious disease PharmD not available for notification 24/7; generalizability limited with antimicrobial team needed; smaller post-PCR group)</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 2 (small sample size)</p>

^a ID, identification; EMR, electronic medical record; PharmD, doctor of pharmacy; rPCR, rapid PCR.

TABLE A9 Evidence and summary table and scoring criteria for reference 28^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Forrest et al. (28)</p> <p>Yr: 2006</p> <p>Publication: J Clin Microbiol</p> <p>Affiliations: University of Maryland School of Medicine, Division of Infectious Diseases School of Dentistry, and Department of Pathology, University of Maryland Medical Center, Department of Pharmacy, Baltimore, MD</p> <p>Funding: not clear for this study; speaker's honoraria and travel support from AdvanDx</p>	<p>Design: pretest vs posttest</p> <p>Facility/setting: University of Maryland Medical Center with AMT team</p> <p>Time period: pretest 2003, posttest 2004</p> <p>Populations/samples: positive BCs were confirmed as yeast by Gram staining; some exclusions</p> <p>Comparator: Quali Test Albicans, a Vitek 2 system germ tube formation, and determination of morphology on cornmeal agar; agar disk diffusion and broth microdilution; yeast-positive BCs were called in to the primary clinical service</p> <p>Study bias: none noted</p>	<p>Description: PNA-FISH; 1 member of the AMT, the infectious diseases attending physician, the fellow on call, or the clinical pharmacist, was notified of all PNA-FISH results</p> <p>Duration: 1 yr</p> <p>Training: not discussed</p> <p>Staff/other resources: antimicrobial management team</p> <p>Cost: start-up outlay of \$1,000 for purchasing a water bath, lens filter, and UV light source microscope, technician time costs (45 min, or \$12 in labor), and the reagent kit's list price of \$68 (\$30 is reimbursed by insurance), with a total cost of \$5,760 for the yr</p>	<p>Description:</p> <p>(i) Broad-spectrum antibiotic use (as DDD)</p> <p>(ii) Total antifungal cost</p> <p>Recording method: clinical and laboratory data; data from pharmacy database; wholesale acquisition costs used to standardize and calculate the costs</p>	<p>Types of findings: pretest vs posttest</p> <p>Findings/effect size:</p> <p>(i) Broad-spectrum antibiotic (casposfungin) use against <i>C. albicans</i>: 8.7 DDDs/patient pretest ($n = 33$) vs 3.2 DDDs/patient posttest ($n = 31$) ($P < 0.05$)</p> <p>(ii) Total antifungal costs/patient with <i>C. albicans</i>: \$169,290 pretest ($n = 33$) vs \$107,942 posttest ($n = 31$)</p> <p>Statistical significance/tests: statistical analysis was performed using the Mann-Whitney test, χ^2 analysis, and Fisher's exact test, where appropriate</p> <p>Results/conclusion biases: small sample size</p>
<p>Quality rating: 7 (fair) (10-point maximum)</p> <p>Effect size magnitude rating: NA (relevance NA)</p>	<p>Study (3-point maximum): 2 (possible limitations in generalizability with AMT needed; large hospital may not generalize to smaller ones)</p>	<p>Practice (2-point maximum): 1 (not clear how quickly AMT member was notified of PNA-FISH results)</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 2 (sample size might be too small for robust estimate of practice)</p>

^a AMT, antimicrobial management team; DDD, defined daily dose.

TABLE A10 Evidence summary table and scoring criteria for reference 59^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Forrest et al. (59) Yr: 2006 Publication: J Antimicrob Chemother Affiliations: Division of Infectious Diseases, University of Maryland School of Medicine; Department of Pharmacy, University of Maryland Medical Center; Department of Pathology, University of Maryland, Baltimore, MD Funding: not clear for this study; speaker's honoraria and travel support from AdvanDx</p>	<p>Design: Retrospective chart review; case-control study Facility/setting: UMMC is a 650-bed tertiary-care medical center and 90-bed shock trauma center; since 2000, rates of MRSA have been >50% of patients Time period: 3 mo in 2004 on initial implementation of PNA-FISH; control group was not tested during 3-mo PNA-FISH period Populations/samples: 53 BCs for PNA-FISH testing and 34 BCs for conventional testing; specimens were from patients on the medical and surgical floors and the ICU Comparator: standard isolation plates; catalase (3% H₂O₂) and latex coagulase tests; GPCC results reported to primary clinical service; vancomycin released pending culture results to doctor and required subsequent AMT intervention with final culture results Study bias: limitations in generalizability; small time period</p>	<p>Description: PNA-FISH; batched daily; second call to primary clinical service of PNA-FISH results; AMT informed of all PNA-FISH results for GPCC; AMT could determine need for vancomycin usage from PNA-FISH results Duration: 3 mo Training: not noted Staff/other resources: antimicrobial management team Cost: minimal, requiring the purchase of a water bath and a lens filter for the UV light source microscope; \$12 labor/batch, \$68/test/patient (reimbursement \$30/sample); costs minimized by batching an avg of 5 specimens</p>	<p>Description: (i) LOS (ii) Broad-spectrum antibiotic use (as DDD) (iii) Overall costs per patient Recording method: for CoNS bacteria; (i) patient LOS obtained from the UMMC's central data repository; (ii) broad-spectrum antibiotic use obtained from the clinical pharmacy and calculated using standard WHO guidelines; (iii) overall patient costs (including pharmacy and laboratory) were obtained from the UMMC's central data repository</p>	<p>Types of findings: control (comparator) (<i>n</i> = 34) vs case (PNA-FISH) (<i>n</i> = 53) Findings/effect size: (i) Median LOS, 6 days (controls) vs 4 days (cases) (<i>P</i> < 0.05; CI, 0.95–1.87 days; RR, 1.33) (ii) The total no. of DDDs of vancomycin/patient: 6.78 to controls vs 4.9 to cases (<i>P</i> = NS); DDDs of vancomycin/patient after GPCC results: 4.8 to controls vs 2.55 to cases (<i>P</i> = 0.06) Patients receiving 0 doses of vancomycin: 9% (3/34) of controls vs 17% (9/53) of cases (<i>P</i> = 0.06) Patients receiving ≤1 dose of vancomycin: 15% (5/34) of controls vs 43% (23/53) of cases (<i>P</i> < 0.005) (iii) Overall cost/patient: \$13,621 for controls vs \$9,616 for cases Statistical significance/tests: Cox hazard analysis, Wilcoxon rank sum (Mann-Whitney) test, Fisher's exact test, and χ^2 test, where appropriate Results/conclusion biases: confounding effect of AMT intervention for PNA-FISH results; confounding effect of AMT with greater ability than with antimicrobial use in PNA-FISH samples; small sample size</p>
<p>Quality rating: 7 (fair) (10-point maximum) Effect size magnitude rating: NA (relevance NA)</p>	<p>Study (3-point maximum): 2 (study bias [see above])</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 1 (sample size too small and time period too short to allow for a robust evaluation of practices; possibly confounding effects [see above]; uncontrolled bias)</p>

^a RR, relative risk; NS, not significant; DDD, defined daily dose.

TABLE A11 Evidence summary table and scoring criteria for reference 56^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Forrest et al. (56)</p> <p>Yr: 2008</p> <p>Publication: Antimicrob Agents Chemother</p> <p>Affiliations: Division of Infectious Diseases, Department of Epidemiology and Preventive Medicine, and Department of Pathology, University of Maryland School of Medicine, and Department of Pharmacy, University of Maryland Medical Center, Baltimore, MD</p> <p>Funding: not clear for this study; speaker's honoraria and travel support from AdvanDx</p>	<p>Design: quasiexperimental study (one group, with pretest and posttest design)</p> <p>Facility/setting: University of Maryland Medical Center; 600-bed inner-city tertiary-care teaching hospital</p> <p>Time period: 2005 (pretest), 2006 (posttest; PNA-FISH)</p> <p>Populations/samples: 129 patients pretest, 95 patients posttest; all patients with hospital-acquired bacteremia due to <i>E. faecium</i> or <i>E. faecalis</i> were included</p> <p>Comparator: standard growth media; catalase detection with 3% H₂O₂ and a pyrrolidonyl arylamidase-positive result; Vitek 2; disc diffusion assay following the CLSI protocols; AMT's action on therapy through clinical factors and final susceptibility results</p> <p>Study bias: experienced lab staff accustomed to performing PNA-FISH test; limited generalizability of the test and the AMT intervention to other medical centers; limited by nonrandomized design; slightly greater severity of illness in PNA-FISH group</p>	<p>Description: PNA-FISH; AMT intervened at time of PNA-FISH results to direct antimicrobial therapy</p> <p>Duration: assumed to be 1 yr</p> <p>Training: not provided; staff were well experienced in PNA-FISH</p> <p>Staff/other resources: AMT, which consists of a full-time infectious disease pharmacist and an infectious disease physician who devotes 25% of his or her time to the AMT</p> <p>Cost: not provided</p>	<p>Description:</p> <p>(i) Time to report identification</p> <p>(ii) Time to targeted therapy</p> <p>(iii) 30-day mortality rate</p> <p>Recording method: chart review; (i) the total time to report the identification was in days from the date the BC specimen was drawn until the microbiological lab report; (median [range]); (ii) the time to appropriate therapy was the period from the time the blood culture was drawn to the time of receipt of appropriate therapy (median [range])</p>	<p>Types of findings: pretest vs posttest</p> <p>Findings/effect size:</p> <p><i>E. faecalis</i> (pretest, <i>n</i> = 64; posttest, <i>n</i> = 48)</p> <p>(i) For the median time to report the identification (range), 4 days (2.4–9.8 days) pretest vs 1.1 days (0.5–3.3 days) posttest (<i>P</i> < 0.001)</p> <p>(ii) The median time to targeted therapy (range) was 0 days (0–5.3 days) pretest vs 0.3 day (0–6.5 days) posttest (<i>P</i> = 1)</p> <p>(iii) 13% (8/64) of patients pretest vs 10% (5/48) of patients posttest (<i>P</i> = 0.73)</p> <p><i>E. faecium</i> (pretest, <i>n</i> = 65; posttest, <i>n</i> = 47)</p> <p>(i) The median time to report an identification (range) was 3.3 days (2.0–8.6 days) pretest vs 1.1 days (0.5–3.3 days) posttest (<i>P</i> < 0.001)</p> <p>(ii) The median time to targeted therapy (range) was 3.1 days (0–9 days) pretest vs 1.3 days (0–4.3 days) posttest (<i>P</i> < 0.001)</p> <p>(iii) For 30-day mortality rate, 45% (29/65) of patients pretest vs 26% (12/47) posttest</p> <p>Statistical significance/tests: categorical variables using the χ^2 or the Fisher exact test; continuous variables using a <i>t</i> test; survival curves of the time to effective antibiotic therapy by a log rank test; all tests were two tailed (<i>P</i> < 0.05)</p> <p>Results/conclusion biases: none noted</p>
<p>Quality rating: 7 (fair) (10-point maximum)</p> <p>Effect size magnitude rating: moderate (direct relevance)</p>	<p>Study (3-point maximum): 1 (study bias and potential generalizability limitations [see above])</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 1 (recording methods not well described)</p>	<p>Results/findings (3-point maximum): 3</p>

^a AMT, antimicrobial management team.

TABLE A12 Evidence summary table and scoring criteria for unpublished data contributed by authors listed^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: D. C. Gamage, D. P. Olson, L. H. Stickell, K. R. Matthias, E. C. Tuttle, D. R. Johnson, C. Valentino, D. E. Nix, N. N. Whitfield, and D. M. Wolk, unpublished</p> <p>Yr: unpublished</p> <p>Publication: NA</p> <p>Affiliations: University of Arizona/BIO5 Institute, Tucson, AZ; University of Arizona Medical Center, Tucson, AZ; University of Arizona/College of Pharmacy, Tucson, AZ</p> <p>Funding: alternate product research support from PNA Traffic Light</p>	<p>Design: pretest vs posttest vs second posttest</p> <p>Facility/setting: University Medical Center, Tucson, AZ; a tertiary-care academic medical center</p> <p>Time period: pretest Aug 2007–Aug 2008; posttest Aug 2008–Mar 2010; 24/7 period Mar 2010–Mar 2011</p> <p>Populations/samples: <i>Enterococcus</i>: pretest $n = 198$; posttest $n = 124$; 24/7 $n = 138$; <i>Candida</i>: pretest $n = 42$; posttest $n = 44$; 24/7 $n = 39$; blood bottles containing GPCPC and Gram stains containing yeast cells selected; no statistically significant difference between groups for most factors, but the pretest group was the least sick for the enterococcus group</p> <p>Comparator: no PNA-FISH used; typical laboratory phenotypic ID practices employed; Gram stain results phoned to physician</p> <p>Study bias: none noted</p>	<p>Description: posttest was PNA-FISH; Gram stain results were phoned to physician; PNA-FISH testing was batched 5 days/wk, with typical phenotypic ID lab practices on the weekend and after 8 p.m. on weekdays; PNA-FISH results called to infectious disease pharmacists 8 a.m.–8 p.m. and to physician 8 p.m.–8 a.m.</p> <p>Duration of posttest: 18 mo; 24/7 study, 1 yr</p> <p>Training: none noted</p> <p>Staff/other resources: medical technologists for PNA-FISH testing; infectious disease pharmacist</p> <p>Cost: not provided</p>	<p>Description:</p> <p>(i) LOS</p> <p>(ii) Mortality</p> <p>(iii) Hospital costs</p> <p>Recording method: data were extracted from the UMC Flowcast database using Crystal Reports 11 software to create 2 separate databases: an enterococcus data set and a candida data set; a Consumer Price Index adjustment was made for hospital costs to 2011 dollars</p>	<p>Types of findings: pretest vs posttest</p> <p>Findings/effect size:</p> <p>For patients with <i>Enterococcus</i>,</p> <p>(i) The LOS pretest was 16.5 days ($n = 159$) and posttest was 19.3 days ($n = 109$); with 24/7 reporting, the LOS was 14.5 days ($n = 118$) ($P = 0.353$)</p> <p>LOS pretest was 16.5 days ($n = 159$); posttest with 24/7 reporting, it was 16.8 days ($n = 227$) ($P = 0.16$)</p> <p>(ii) Mortality pretest was 13.13% (26/198) of patients; mortality posttest was 8.06% (10/124) of patients; with 24/7 reporting, mortality was 7.97% (11/138) of patients ($P = 0.20$)</p> <p>Mortality pretest was 13.13% (26/198) of patients; posttest with 24/7 reporting, it was 8% (21/262) ($P = 0.09$)</p> <p>In the logistic regression model, the OR (95% CI) for:</p> <p>24/7 vs pretest, 0.53 (0.234–1.132) by χ^2 test ($P = 0.10$)</p> <p>24/7 vs posttest, 0.94 (0.370–2.387) by χ^2 ($P = 0.89$)</p> <p>Posttest vs pretest, 0.57 (0.248–1.212) by χ^2 ($P = 0.15$)</p> <p>Pretest vs posttest vs 24/7 L-R ($P = 0.18$)</p> <p>(iii) The hospital cost pretest was \$102,076 ($n = 159$) vs \$106,063 posttest ($n = 109$) vs \$48,735 with 24/7 reporting ($n = 118$) ($P = 0.09$)</p> <p>The hospital cost pretest was \$102,076 ($n = 159$) vs \$76,263 posttest with 24/7 reporting ($n = 227$) ($P = 0.83$)</p> <p>For patients with <i>Candida</i>,</p> <p>(i) The LOS pretest was 21.9 days ($n = 42$) and posttest was 17 days ($n = 44$) vs 20.1 days with 24/7 reporting ($n = 39$) ($P = 0.773$)</p> <p>The LOS pretest was 21.9 days ($n = 42$) vs 18.6 days posttest with 24/7 reporting ($n = 83$)</p> <p>(ii) Mortality pretest was 26.83% (13/42) of patients vs 20.45% (9/44) posttest vs 7.69% (3/39) 24/7 reporting ($P = 0.063$)</p> <p>The logistic regression model OR (95% CI) was:</p> <p>0.534 (0.234–1.132) with 24/7 reporting vs pretest by χ^2 test ($P = 0.103$)</p> <p>0.940 (0.370–2.387) with 24/7 reporting vs posttest by χ^2 test ($P = 0.895$)</p> <p>0.568 (0.248–1.212) posttest vs pretest by χ^2 test ($P = 0.147$)</p> <p>Pretest vs posttest vs 24/7 reporting with L-R ($P = 0.176$)</p> <p>(iii) The hospital costs pretest were \$188,234 ($n = 42$) vs \$121,544 posttest ($n = 44$) vs \$122,793 with 24/7 reporting ($n = 39$) ($P = 0.312$)</p> <p>The hospital costs pretest were \$188,234 ($n = 42$) vs \$122,131 posttest with 24/7 reporting ($n = 83$) ($P = 0.16$)</p> <p>Statistical significance/tests: Qualitative outcomes were analyzed with Pearson's χ^2 test, Fisher's exact tests, or logistic regression. The logistic regression model for mortality included several adjustments for confounding variables. A descriptive analysis of quantitative data and cost showed that it was uniformly right skewed, so Kruskal-Wallis's one-way ANOVA was used to determine differences</p> <p>Results/conclusion biases: confounding of practices with PNA-FISH and calling of PNA-FISH results to infectious disease pharmacist or physician</p>
<p>Quality rating: 7 (fair) (10-point maximum)</p> <p>Effect size magnitude rating: substantial (less-direct relevance)</p>	<p>Study (3-point maximum): 3</p>	<p>Practice (2-point maximum): 1 (not clear how quickly results were phoned to physician and/or infectious disease pharmacist and if that time was consistent across groups)</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 1 (uncontrolled bias)</p>

^a GPCPC, Gram-positive cocci in pairs and chains; L-R, logistic regression.

TABLE A13 Evidence summary table and scoring criteria for unpublished data contributed by authors listed (now published as reference 58)

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Heil et al., unpublished Yr: unpublished Publication: NA Affiliations: Department of Pharmacy, University of Maryland Medical Center; Department of Pharmacy, Clinical Microbiology-Immunology Laboratory, and Department of Hospital Epidemiology, UNC Health Care; Department of Biostatistics, UNC School of Public Health; and Department of Pathology and Laboratory Medicine, UNC School of Medicine Funding: none noted</p>	<p>Design: pretest vs posttest Facility/setting: not provided Time periods: pretest, 26 June 2009–19 Sept 2010; posttest, 20 Sept 2010–13 June 2011 Populations/samples: pretest $n = 61$, posttest $n = 21$; patients with positive BCs; only first episode of candidemia per patient was analyzed; no statistically significant difference between groups Comparator: combination of CHROMagar <i>Candida</i> and API 20C; organism identification reported only in the electronic medical record Study bias: generalizability limitations</p>	<p>Description: PNA-FISH; BCs positive for yeast in patients who had PNA-FISH performed as part of the antimicrobial stewardship protocol; PNA-FISH performed 7 a.m.–8:30 p.m. 7 days/wk; lab personnel paged on-call pharmacist with results, and pharmacist made a recommendation to medical service based on institution-specific antibiogram for <i>Candida</i> Duration: 9 mo Training: none noted Staff/other resources: none provided Cost: none provided</p>	<p>Description: (i) Time to targeted therapy (ii) LOS (iii) Mortality Recording method: for <i>Candida</i> species, (i) the time to targeted therapy was defined as time (in days) from the blood culture becoming positive for yeast to dispensation of targeted therapy; (ii, iii) for LOS and mortality, this information was not provided</p>	<p>Types of findings: pretest vs posttest Findings/effect size: Pretest $n = 61$, posttest $n = 21$ (i) The mean time to targeted therapy (95% CI) was 2.3 days (1.4–3.2 days) pretest vs 0.6 days (–0.01–1.16 days) posttest ($P = 0.0016$) (ii) The median LOS (interquartile range) was 25 days (16–33 days) pretest vs 12 days (9–30 days) posttest ($P = 0.82$) (iii) Mortality was 31% (19/61) of patients pretest vs 24% (5/21) posttest ($P > 0.99$) Statistical significance/tests: P values were two tailed and determined by the log-rank test for time to targeted therapy and LOS; Fisher's exact test for mortality Results/conclusion biases: small sample size; confounding effect of PNA-FISH and call to pharmacist intervention implemented at the same time</p>
<p>Quality rating: 7 (fair) (10-point maximum) Effect size magnitude rating: substantial (direct relevance)</p>	<p>Study (3-point maximum): 2 (study bias; facility not described; possible generalization concerns with antimicrobial stewardship program)</p>	<p>Practice (2-point maximum): 1 (description of antimicrobial stewardship program lacking; length of time from PNA-FISH results to call to pharmacist not described)</p>	<p>Outcome measures (2-point maximum): 2 (recording method not well described)</p>	<p>Results/findings (3-point maximum): 2 (small sample size)</p>

TABLE A14 Evidence summary table and scoring criteria for reference 57^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Ly et al. (57) Yr: 2008 Publication: Ther Clin Risk Manag Affiliations: Section of Infectious Diseases, Washington Hospital Center, Washington, DC Funding: none noted</p>	<p>Design: Prospective, randomized controlled study; control and intervention groups Facility/setting: Washington Hospital Center is a 907-bed tertiary-care medical center in Washington, DC Time period: 22 Mar 2006–31 Oct 2006 Populations/samples: 101 patients in control group (no LCL), 101 patients in intervention group (LCL intervention); patients blindly randomized 1:1; blood cultures repeatedly positive for GPCC counted only once Comparator: PNA-FISH with no intervention by LCL Study bias: higher mean index for control patients with CoNS than for the intervention group</p>	<p>Description: PNA-FISH; PNA-FISH performed twice daily on all GPCC BCs; results were entered into the LIS, and a list with results was faxed twice daily to the LCL; the LCL notified the treating clinician of results and provided general information on the organism isolated within 3 h of PNA-FISH performance Duration: 7 mo Training: none noted Staff/other resources: LCL Cost: not provided</p>	<p>Description: (i) Overall hospital costs (ii) LOS (iii) Mortality Recording method: medical records of enrolled patients were abstracted for length of hospitalization, and mortality</p>	<p>Types of findings: case vs control Findings/effect size: (i) The median overall hospital charges were \$92,373.78 for the controls vs \$72,932.41 for the intervention group ($P = 0.09$) (ii) The median LOS was 9 days for the controls vs 9 days for the intervention group (iii) Mortality in the control group was 16.8% (17/101) of patients vs 7.9% (8/101) in the intervention group ($P = 0.05$) Statistical significance/tests: medians of outcome variables were compared using the Wilcoxon rank sum test Results/conclusion biases: none noted</p>
<p>Quality rating: 7 (fair) (10-point maximum) Effect size magnitude rating: substantial (less-direct relevance)</p>	<p>Study (3-point maximum): 2 (study bias [see above]; potential generalizability limitations with LCL; short time period)</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 1 (measurement period may be insufficient; small sample size; uncontrolled bias)</p>

^a LCL, laboratory/clinician liaison; GPCC, Gram-positive cocci in clusters; LIS, laboratory information system.

TABLE A15 Evidence summary table and scoring criteria for unpublished data contributed by author listed^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Author: D. Uettwiller-Geiger, unpublished Yr: unpublished Publication: NA Affiliations: Department of Laboratories, John T. Mather Memorial Hospital, Port Jefferson, NY Funding: none noted; presented as a case study on Cepheid's website</p>	<p>Design: pretest vs posttest Facility/setting: John T. Mather Memorial Hospital is a 248-bed not-for-profit hospital in Port Jefferson, NY Time period: pretest, 2007; posttest, Mar 2008–2009 Populations/samples: at-risk populations of the ICUs, CCU, and Department of Orthopedics and later expanded to the telemetry unit; 1,050 tests in 2008, 1,201 tests in 2009 Comparator: not provided; presumed typical lab techniques Study bias: pretest vs posttest time periods might allow for information bias over time; confounding effect of active surveillance program introduced at same time as PCR testing</p>	<p>Description: PCR; GeneXpert system; rapid active screening and surveillance for MRSA initiative, which includes immediate, real-time alert by fax and phone from lab to preventionists; 24/7 testing using PCR Duration: 2 years (assumed based on years noted in poster) Training: none noted Staff/other resources: multidisciplinary group of senior leadership, infection preventionists, clinicians, finance, and environmental services; no additional FTE required for PCR testing 24/7 Cost: ~\$63/test, fully burdened, for PCR assay</p>	<p>Description: (i) Hospital costs (ii) LOS (in ICU and CCU) Recording method: results related to MRSA infections; (i) hospital costs were calculated based on the avg cost of infection incurred during hospitalized medical care of \$35,000/infected patient</p>	<p>Types of findings: pretest vs posttest Findings/effect size: (i) The hospital decreased the cost of infection by \$920,500 in 2008 and by \$847,000 in 2009 and almost \$1.8 million between 2007 and 2009; 50% reduction in costs (ii) 9.3% decrease in LOS from 2008 to 2009 (3.75 days in 2008 to 3.4 days in 2009) Statistical significance/tests: none noted Results/conclusion biases: confounding factors from MRSA screening program implemented at same time</p>
<p>Quality rating: 7 (fair) (10-point maximum) Effect size magnitude rating: NA (relevance NA)</p>	<p>Study (3-point maximum): 2 (study bias [see above])</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 1 (no statistical comparison of results; uncontrolled bias)</p>

^a ICUs, intensive care units; CCU, cardiac care unit; FTE, full-time employee.

TABLE A16 Evidence summary table and scoring criteria for reference 62^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Bruins et al. (62) Yr: 2005 Publication: Eur J Clin Microbiol Infect Dis Affiliations: Laboratory of Clinical and Microbiology and Infectious Disease, Institute for Health Policy and Management, Erasmus University of Rotterdam; Department of Medical Microbiology, University of Gronigen, The Netherlands Funding: bioMérieux and Stichting Zorg op Regionale Grondslag</p>	<p>Design: Prospective, single-blind, controlled, randomized study Facility/setting: Isala Klinieken hospital, a multisite 1,100-bed tertiary-care teaching hospital in Zwolle, The Netherlands Time period: SP1–Sept–Nov 2000; SP2–Dec 2000–Feb 2001; SP3 Mar–June 2001 Populations/samples: 1,883 inpatients with confirmed bacterial infection by <i>Enterobacteriaceae</i>, <i>Pseudomonas aeruginosa</i>, <i>Staphylococcus</i> spp., and <i>Enterococcus</i> spp.; exclusions Comparator: conventional, overnight methods for ID (API system) and AST (disc diffusion) Study bias: no LIS; results communicated on paper; not all specimens were blood cultures (SP1, <i>n</i> = 34 vs 37 total; SP2, <i>n</i> = 29 vs 28; SP3, <i>n</i> = 25 vs 30); relied on discretion of microbiologist to make a call for direct communication; resistance was generally low, comparable to that in United States</p>	<p>Description: Vitek 2 (bioMérieux) for ID (2–3 h) and AST (5.5–19 h); in SP1, Vitek 2 was used for rapid testing, reporting was the same for practice and comparator tests, and hard-copy results were dispatched; in SP2, Vitek 2 was used with oral reporting of AST results, with a dial-up connection to obtain Vitek 2 results after normal business hours and report directly to the clinician; hard-copy results were dispatched as in SP1; in SP3, the same methods used in SP2 were repeated, with the lab work day extended by 1 h (with a start time 1 h earlier) and also an extra mail delivery at the end of the day to deliver hard copies directly to attending staff Duration: 9 mo (3 mo/study period) Training: none noted Staff/other resources: 3 medical doctor clinical microbiologists were in charge of lab Cost: not provided</p>	<p>Description: (i) Mortality (ii) LOS (iii) LOS in ICU (iv) Cost of antimicrobial agents (v) Time to report from sample arrival and oral reporting of final AST (vi) Time to report from sample arrival and dispatch of final hard-copy results (vii) Time to targeted therapy Recording method: hospital records; time points for sample processing were recorded; receipt of hard copy recorded on questionnaires; medical charts; (iv) the cost of antimicrobial agents was in Euros; (vii) the time interval between sample arrival and the first change in antibiotic therapy was recorded thereafter</p>	<p>Types of findings: study phase vs comparator Findings/effect size: (i) For mortality in SP1, (38/294 [12.9%]) vs comparator (30/320 [9.4%]) (<i>P</i> = 0.161); in SP2, (37/303 [12.2%]) vs comparator (44/317 [13.9%]) (<i>P</i> = 0.538); in SP3, (29/308 [9.4%]) vs comparator (44/328 [13.4%]) (<i>P</i> = 0.114) (ii) For LOS (days), in SP1, (15 [8–30]) vs comparator (17 [8–29]) (<i>P</i> = 0.676); in SP2, (15 [7–30]) vs comparator (17 [8–32]) (<i>P</i> = 0.608); in SP3, (17 [9–35]) vs comparator (14 [8–31]) (<i>P</i> = 0.210) (iii) For LOS in ICU (days [range]), in SP1, (7.0 [2.3–13.8]) vs comparator (6.5 [3.0–16.0]) (<i>P</i> = 0.722); in SP2, (6.0 [3.0–17.0]) vs comparator (11.0 [4.0–22.0]) (<i>P</i> = 0.174); in SP3, (6.0 [2.0–14.0]) vs comparator (5.0 [2.0–16.5]) (<i>P</i> = 0.840) (iv) For the cost of antimicrobial agents (in Euros), in SP1, (12.2 [0.3–56.5]) vs comparator (8.2 [0.2–54.3]) (<i>P</i> = 0.629); in SP2, (11.3 [0.7–72.7]) vs comparator (9.8 [0.3–54.9]) (<i>P</i> = 0.636); in SP3, (11.0 [1.2–83.9]) vs comparator (11.2 [0.4–61.8]) (<i>P</i> = 0.428) (v) For the time to report the sample arrival and oral reporting of final AST (in hours) (median [IQR]), in SP1 (<i>n</i> = 42) vs comparator (<i>n</i> = 43) (49.4 [30.0–58.6]) vs (52.8 [48.0–76.8]) (<i>P</i> = 0.032); in SP2, (<i>n</i> = 101) vs comparator (<i>n</i> = 53), (45.5 [31.0–64.1]) vs (68.0 [52.0–77.0]) (<i>P</i> < 0.00); in SP3, (<i>n</i> = 52) vs comparator (<i>n</i> = 37), (49 [30.1–75.0]) vs (53.3 [50.0–76.9]) (<i>P</i> = 0.020) (vi) For the time to report from sample arrival and dispatch of final hard-copy results (in hours) (median [IQR]), in SP1, (<i>n</i> = 291) vs comparator (<i>n</i> = 310), (76.0 [52.0–100.0]) vs (78.0 [52.0–115.1]) (<i>P</i> = 0.433); in SP2, (<i>n</i> = 303) vs comparator (<i>n</i> = 316), (93.0 [69.0–103.0]) vs (86.0 [53.0–122.0]) (<i>P</i> = 0.715); in SP3, (<i>n</i> = 301) vs comparator (<i>n</i> = 324), (71.0 [47.5–100.0]) vs (76.0 [52.0–103.0]) (<i>P</i> < 0.00) (vii) For time to targeted therapy (in hours) (median [IQR]), in SP2, (27.0 [7.5–86.5]) vs comparator (49.0 [13.0–94.0]) (<i>P</i> = 0.028); the differences between SP1 and SP3 were not significant Statistical significance/tests: the significance level was 5% (two tailed); χ^2 tests, Fisher's exact tests, and Student's <i>t</i> tests were used to compare clinical impact variables and Mann-Whitney tests to compare time intervals; <i>t</i> tests were performed after natural log transformation for nonnormal data Results/conclusion biases: Mix of BC and other samples</p>
<p>Quality rating: 7 (fair) (10-point maximum) Effect size magnitude rating: substantial (direct relevance)</p>	<p>Study (3-point maximum): 1 (generalizability concerns; study bias)</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 2</p>	<p>Results/findings (3-point maximum): 2 (bias)</p>

^a LIS, laboratory information system; SP1, SP2, and SP3, study phases 1, 2, and 3, respectively.

TABLE A17 Evidence summary table and scoring criteria for reference 63^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Doern et al. (63) Yr: 1994 Publication: J Clin Microbiol Affiliations: Department of Hospital Laboratory and Division of Infectious Diseases, University of Massachusetts Medical Center Funding: grant from MicroScan Division of Baxter Diagnostics, Inc.</p>	<p>Design: Randomized controlled study Facility/setting: University of Massachusetts Medical Center; tertiary-care, teaching medical center Time period: 1 yr Populations/samples: inpatients assigned to practice group (RAST) ($n = 273$) or comparator group (ONAST) ($n = 300$) based on last name; only <i>S. aureus</i>, non-aureus staphylococci, <i>Acinetobacter</i> spp., or <i>Enterobacteriaceae</i> infections were included Comparator: ID and susceptibility tests were performed using traditional overnight techniques; tests were initiated between 9 and 10 p.m. on the day of recognition of bacterial growth; test results were available the next morning; results were telephoned to the clinician as soon as available; all other results were reported to the LIS; hard copies of results were distributed to patient medical records between 2 and 5 a.m. the day after they were available Study bias: only certain bacterial infections were included; only 42 in RAST and 45 in ONAST groups were BCs; more patients in the RAST group had underlying fatal disease than in the ONAST group; significantly more patients in the RAST group had line-related bacteremia than in the ONAST group</p>	<p>Description: ID and AST were performed using the Baxter-MicroScan Walkaway-96 system (2–7 h); ID and susceptibility tests were initiated immediately upon recognition of bacterial growth (between 8 and 11 a.m.); test results were available the same day; results were telephoned to the clinician as soon as they were available; results were also transferred to the lab computer immediately for direct clinician access; hard copies of results were distributed to patient medical records between 2 and 5 a.m. the day after they were available Duration: 1 yr Training: not noted Staff/other resources: not noted Cost: not noted</p>	<p>Description: (i) LOS (ii) LOS after positive culture (iii) Mortality (iv) Time to report (v) Cost (vi) Time to targeted therapy Recording method: not provided; (i) mean total length (days) of hospitalization; (ii) mean length of hospitalization following positive culture; (iii) total no. of patient deaths; (iv) mean length of time to definitive ID and avg time period required before susceptibility results available; (v) total cost; (vi) mean length of time from positive culture to change in therapy</p>	<p>Types of findings: comparison of RAST ($n = 273$) vs ONAST ($n = 300$) groups Findings/effect size: (i) The mean LOS (range [SD]) is 20.7 days (2–129 [20.7] days) vs 20.1 days (2–133 [20.0] days) (the differences are NS) (ii) The mean LOS after a positive culture (range [SD]) is 14.7 days (0–118 [17.6] days) vs 14.6 days (1–118 [16.5] days) (the differences are NS) (iii) The mortality was 24/273 (8.8%) vs 46/300 (15.3%) ($P = 0.016$) (iv) The mean time until an ID was received (range [SD]) was 11.3 h (0.5–77 [14.4] h) vs 19.9 h (0.5–101 [15.5] h) ($P < 0.0005$); the time to a determination of susceptibility was 9.6 h (4–68 [13.2] h) vs 25.9 h (16–78 [11.0] h) ($P < 0.0005$) (v) The mean total cost (range [SD]) was \$15,062 (\$1,165–\$26,0187 [\$17,661]) vs \$19,256 (\$1,780–\$298,975 [\$21,644]) ($P = 0.0118$) (vi) The mean length of time from a positive culture to a change in therapy was 16.3 h vs 31.2 h ($P < 0.0005$) Statistical significance/tests: paired t tests, χ^2 analysis, and Fisher's exact test Results/conclusion biases: mix of BCs and other samples; sample size for BC was small</p>
<p>Quality rating: 6 (fair) (10-point maximum) Effect size magnitude rating: substantial (direct relevance)</p>	<p>Study (3-point maximum): 2 (study population bias)</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 1 (recording methods were not well defined)</p>	<p>Results/findings (3-point maximum): 1 (bias)</p>

^a LIS, laboratory information system.

TABLE A18 Evidence summary table and scoring criteria for reference 61^a

Bibliographic information	Study	Practice	Outcome measures	Results/findings
<p>Authors: Kerremans et al. (61)</p> <p>Yr: 2008</p> <p>Publication: J Antimicrob Chemother</p> <p>Affiliations: Department of Medical Microbiology and Infectious Diseases, Institute for Medical Technology Assessment, and Department of Epidemiology and Biostatistics, Erasmus University Medical Centre, Rotterdam, The Netherlands</p> <p>Funding: grant from Dutch Association of University Hospitals and bioMérieux</p>	<p>Design: prospective randomized clinical trial</p> <p>Facility/setting: Erasmus Medical Center; 1,200-bed tertiary-care university medical center in The Netherlands; integrated laboratory and active 24/7 consultation service by medical microbiologists and infectious disease specialists; weekend lab hours</p> <p>Time period: 2 yr, from Feb 2001–Mar 2003</p> <p>Populations/samples: inpatients with positive culture growth from tested body fluid; <i>n</i> = 746 for practice and <i>n</i> = 752 for comparator; bacteria and fungi were evaluated</p> <p>Comparator: overnight Vitek 1 system; results were reported to the infectious disease consultation service from 10:30 a.m.–5 p.m.</p> <p>Study biases: infectious disease consultants were not blind to randomization; not all samples were BCs; there were few BSIs compared to other infections in the study; low level of antibiotic resistance in hospital</p>	<p>Description: rapid (intervention) testing using Vitek 2 for ID and AST; positive BCs tested directly on Vitek 2 without subculturing; remote access to Vitek 2 in evening hours; results phoned immediately to infectious disease consultation service from 10:30 a.m.–11 p.m.</p> <p>Duration: 2 yr</p> <p>Training: not provided</p> <p>Staff/other resources: 24/7 consultation service; weekend lab hours; technician on call on evening and night shifts</p> <p>Cost: not provided</p>	<p>Description:</p> <p>(i) Mortality</p> <p>(ii) Broad-spectrum antibiotic use</p> <p>(iii) Time to targeted therapy</p> <p>(iv) Time to report results</p> <p>Recording method: 4-wk follow-up period; hospital information system; municipal population register (for mortality after discharge) and manually from patient files; (ii) for broad-spectrum antibiotic use, including day therapy, the times that DDDs were started and stopped were recorded; (iii) for the time to targeted therapy, a change to a different antibiotic agent was recorded, with the date of the new antibiotic agent defined as the switch date; (iv) the time to report an ID and AST result after positive culture growth was detected was recorded for Bactec cultures only</p>	<p>Types of findings: comparison of practice vs comparator</p> <p>Findings/effect size:</p> <p>(i) For mortality, 130/739 (17.6%) patients vs 112/738 (15.2%) (<i>P</i> = 0.21; 95% CI, –1.6%, 6.1%)</p> <p>(ii) For broad-spectrum antibiotic use (DDD) (SD), the practice group <i>n</i> = 497 and the comparator group <i>n</i> = 503; for total antibacterials, 23.9 (21.5) days vs 27.9 (24.7) days (<i>P</i> = 0.020; 95% CI, 1.2–6.9); for antifungals, 2.7 (9.9) days vs 4.9 (16.5) days (<i>P</i> = 0.050; 95% CI, 0.5–3.9); for total antibacterials + antifungals, 26.6 (24.5) days vs 32.9 (31.9) days (<i>P</i> = 0.012)</p> <p>(iii) For the time until targeted therapy was begun, the day of randomization included 90 switches vs 60 switches (<i>P</i> = 0.006); on day 2 after randomization, there were 42 switches vs 24 switches (<i>P</i> = 0.019)</p> <p>(iv) The times to report an ID were 18.9 h vs 33.4 h (<i>P</i> < 0.0001); the times to report an AST result were 19.4 h vs 39.8 h (<i>P</i> < 0.0001)</p> <p>Statistical significance/tests: power calculations were performed; <i>t</i> tests for TATs; χ^2 test for antibiotic therapy switches; Mann-Whitney for DDDs</p> <p>Results/conclusion biases: samples included various body fluids, not only blood; small no. of bloodstream infections; broad-spectrum antibiotic use results were confounded by inclusion of all antibiotics used during study; not clear that the ID and AST result times provided for the comparator included the time to report results</p>
<p>Quality rating: 6 (fair) (10-point maximum)</p> <p>Effect size magnitude rating: substantial (direct relevance)</p>	<p>Study (3-point maximum): 2 (study bias and generalizability concerns)</p>	<p>Practice (2-point maximum): 2</p>	<p>Outcome measures (2-point maximum): 1 (cannot separate BSIs from other cultures)</p>	<p>Results/findings (3-point maximum): 1 (biases, small BSI sample size)</p>

^a DDD, defined daily doses; TATs, turnaround times.

TABLE A19 Evidence summary table and scoring criteria for reference 60

Bibliographic information	Study	Practice	Outcome measures	Results/findings
Authors: Trenholme et al. (60) Yr: 1989 Publication: J Clin Microbiol Affiliations: Section of Infectious Disease, Department of Internal Medicine, Section of Clinical Microbiology, Offices of Consolidated Laboratory Services, and Department of Immunology/Microbiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL Funding: none noted	Design: randomized trial Facility/setting: not provided Time period: 11 mo Populations/samples: $n = 110$ for practice vs $n = 116$ for comparator; exclusions; various organisms included; inpatients with positive blood cultures were randomly assigned to an arm of the study Comparator: routine lab methods for ID and AST; blood agar plate growth followed by Micro-ID strip or MicroScan Combo panel; tube coagulase; physician informed by infectious disease fellow of ID and AST results as soon as available; infectious disease fellow recommended initiation or alterations in therapy Study bias: high rate of noncompliance with therapeutic recommendations by doctors for patients under routine method arm	Description: direct inoculation of Vitek AutoMicrobic system; cytochrome oxidase on Gram-negative rods and tube coagulase on Gram-positive cocci; physician informed by infectious disease fellow of ID and AST results as soon as available; infectious disease fellow recommended initiation or alterations in therapy Duration: 11 mo Training: none noted Staff/other resources: none noted Cost: not provided	Description: (i) Time to report ID (ii) Reduction in broad-spectrum antibiotic use Recording method: not provided; (i) the time to report an ID assumes that results were reported immediately upon collection; (ii) for a reduction in broad-spectrum antibiotic use, a percentage of the population was changed to an effective therapy, and a percentage of the population discontinued antibiotics	Types of findings: comparison of practice ($n = 110$) and comparator ($n = 116$) Findings/effect size: (i) The avg time to report an ID (range) for Gram-positive cocci was 10.6 h (4–15 h); the avg time to report an AST result was 6.6 h (4–10 h); for Gram-negative rods, for an ID, 5.8 h (4–18 h), and for an AST result, 5.9 h (4–10 h); overall for an ID, 8.8 h vs 48 h; overall for an AST result, 6.4 h (ii) For a reduction in broad-spectrum antibiotic use, the no. of patients changed to an effective therapy was 8/110 (7.3%) vs 1/116 (0.9%) ($P < 0.05$); the no. of patients who discontinued therapy was 6/110 (5.5%) vs 4/116 (3.4%) Statistical significance/tests: not provided Results/conclusion biases: high rate of noncompliance with therapeutic recommendations by doctors for patients under the routine method arm
Quality rating: 6 (fair) (10-point maximum) Effect size magnitude rating: moderate (direct relevance)	Study (3-point maximum): 2 (facility not described; bias)	Practice (2-point maximum): 1 (relaying of results not well described)	Outcome measures (2-point maximum): 1 (recording method not described)	Results/findings (3-point maximum): 2 (bias)

APPENDIX 6

LMBP Evaluation of Rapid Methods for Bloodstream Infection Identification: Suggested Roadmap for Future Quality Improvement Studies

Analysis of quality improvement study data for the purpose of a systematic review of evidence about laboratory practice effectiveness requires that some basic and essential parameters of study design be included, documented, and adequately described by laboratory investigators for more standard reporting and comparison (meta-analysis). This document is developed as a roadmap to organize, plan, and report a quality improvement project to address the following questions. For hospital inpatients with bloodstream infections (e.g., positive blood cultures), what practices are effective at increasing the timeliness of providing targeted therapy, and do these practices improve the patient's clinical outcome?

In general, the design, description, methods, data collection, and analysis for the study should be written and documented for replication by other laboratory investigators, with provision of results to verify or refute the original study. The following roadmap may be a useful outline for a study of this topic as well as guide data collection for a quality improvement project responsive to the evaluated practices of this review.

Figures A1 and A2 show a data collection form including the criteria to consider and address when planning, conducting, and reporting this type of QI study. It may assist in addressing the questions to be asked and in defining the population, interven-

tion, comparison, and outcome (PICO) elements that should be included as part of an evidenced-based QI study.

Background Information

- A. Usual (comparison) practices. This roadmap provides examples of traditional, rapid, or phenotypic identification techniques for BSIs and other laboratory practices, such as reporting, classification of testing personnel, and testing schedule, that are currently performed at your facility. Use the roadmap to select which of these elements your facility is currently following to identify and report bloodstream infections for inpatients.
 1. Laboratory test. In this checklist, identify the usual testing method(s) used by your facility. If your testing method is not listed, please add it in the Other space. Note that if your lab is currently using blood cultures for BSI testing, please indicate (if the data are available) the percentage of positive blood cultures, the percentage of contaminated blood cultures, and the percentage of bottles with optimal fill volume. Also, include the average time from the collection of blood cultures to arrival in the laboratory and the average time from when positive blood cultures are removed from the instrument to when Gram staining is performed.
 2. Laboratory reporting. Currently, how does your facility communicate positive bloodstream reports for in-

Background Information	Quality Improvement Study	QI Practice	Outcome Measures	Results/Findings
A. Usual (Comparator) Practice* 1) Laboratory Test Blood Culture and routine reporting practice PNA FISH Real-time PCR Chromogenic agar Rapid Vitek 2 Pneumostide Latex Direct Mass Spectrometry Rapid Gram Stain Other _____ Other Background Information ___ % Positive Blood Culture (BC) ___ % Blood Culture Contamination ___ % Optimal Blood Culture fill volume ___ Avg. time to BC bottles delivery to lab ___ Avg. time of Positive BC bottle removal 2) Laboratory Reporting Direct call/page to ID physician Direct call/page to non-ID physician Direct call/page to ID pharmacy Direct call/page to general pharmacy Direct call to other _____ Report to LIS _____ other defined _____ 3) Testing Personnel Medical Laboratory Scientist (4yr) Medical Laboratory Technician(2yr) Research staff Other - Describe: _____ 4) Testing Schedule Days batch or non-batch (circle) Evening batch or non-batch (circle) Night batch or non-batch (circle) No weekends Other - Describe _____ B. Funding Source(s): In-house Manufacturer: Describe: Grant/Contract: Describe: None Other _____ Describe †	C. QI Study Design/Type: Pre-post implementation Split implementation (different intervention at different units or locations) Randomized study Multi-site(or multiple organization) Other, please describe on pg. 2 D. Human Subjects 1) Patient Population (check all that apply), Pediatric Adult Women Minorities Other protected subjects 2) Age/Gender 3) IRB approved? (Yes No) E. Facility Description Hospital Size (#Beds) Hospital/Laboratory Type* Community Regional Academic Veteran's Affairs For-profit Healthcare group Reference laboratory Other _____ F. Study Setting * In-patient ICU Geriatric Cancer Center Other (describe) G. Sampling Strategy Sample Size for Usual practice: _____ Sample Size for Alternate practice: _____ Organisms _____ Sample description: Census, Random or Convenience sampling(circle) Other _____	H. Alternate/Intervention Practice: Blood Culture and routine reporting practice PNA FISH Real-time PCR Chromogenic agar Rapid Vitek 2 Pneumostide Latex Direct Mass Spectrometry Rapid Gram Stain Other _____ I. Scheduled Study Dates List start and end dates of each phase : Pilot: start _____ end _____ Pre: start _____ end _____ Post: start _____ end _____ Other QI Study: start _____ end _____ start _____ end _____ J. Data collection: Retrospective Prospective Both K. Exclusions? Duplicates Autopsy Other _____ L. Resource Requirements/Costs: A. Staff / Training: B. Equipment: C. Supplies: D. Other :	M. Outcome Measure(s) Description : Time to report Gram's stain result Time to report Other Rapid Test ID Time to report Traditional ID Time to targeted therapy Additional blood cultures collected Additional laboratory tests, other Time of empiric (initial) therapy Length of Stay (days/hospital visit) N. Other Possible Measures (examples): Total Costs, per visit Antibiotic costs, per visit % Antibiotic resistance % Hospital acquired infections APACHE Score SOFA Score Other _____ Describe † O. Recording method † Log of occurrences Incident / adverse events reports Audit - direct observation Electronic information system monitoring Other _____ Please describe each checked method and the outcome measure. †	Q. Results/Findings† (additional space on pg.2): 1) Additional Information DRG or primary disease Co-morbidities R. Unanticipated Changes During Implementation List any factors which may have influenced the results of this study; such as new activities or changes introduced and ongoing during the same time as the study. _____ _____ *Check all that apply †Use additional pages as required

FIG A1 Chart to assist in planning future QI studies.

† Additional page for items requiring further description:

B. Funding Source(s):
 If there are other funding sources than those included in the list please describe the source:

C. QI Study Design/Type:
 Describe the study designed used for your QI project if it is not listed on page 1-

G. Sampling Strategy:
 Describe the your sampling strategy if it is not included on page 1-

N. Other Possible Measures (examples):
 If your project included additional findings under outcome measures other than those on page 1 please describe

O. Recording Methods:
 Add a complete description on how each checked item was recorded and which outcome measure it represented on page 1.

Q. Result/Findings:

FIG A2 Second page of chart in Fig. A1 for items requiring further description.

patients? If the reporting protocol requires a direct call/page to the identified physician as well as reporting to the laboratory information systems (LIS), check both boxes. Additional spaces are provided if another practitioner is called or another protocol is followed.

- Testing personnel. Check which testing personnel are involved in completion of the patient testing at your facility. If a laboratory assistant preforms the preliminary lab set-up, such as preparation of Gram stain, but the reading and reporting of the test is conducted by the medical technologist please indicate the personnel for the final assessment of the test.
- Testing schedule. Indicate your current schedule for testing bloodstream specimens. If testing is conducted on a 24-h schedule, please circle all options that apply (days, evening, and night). Also, indicate the frequency of testing by circling "batch" or "non-batch."
- Funding source(s) (if applicable). List who may have assisted you financially in this quality improvement project for purposes of reporting in the final published account.

Quality Improvement Study

- Quality improvement study design/type. For planning purposes, select the quality improvement study type. For the

BSI study, a pre/postimplementation design may easily capture the data needed for analysis. In this section, describe the methods/approaches that your facility will use. To limit bias (see the glossary in Appendix 2 and below), use similar patient population characteristics (age range, sex, ethnicity, and diagnosis). Pre/postimplementation measures outcomes of the usual testing practice (preimplementation) and measures outcomes after implementation of the alternate (intervention) practice (postimplementation). “Split implementation” means implementation of different interventions at different locations within the same institution. Your study may be a randomized, controlled study. A multisite trial (multiple facilities) consists of a coordinated series of trials across multiple institutions; i.e., the same research protocol is implemented in several sites. Studies of other formats should be described.

Bias is the tendency to produce results that depart systematically from the “true” results. Bias is any nonrandom factor in the conduct of a study that can influence the results of a study. Four types of bias found in QI projects are selection/allocation, performance, measurement/detection, and attrition/exclusion (see <http://bmg.cochrane.org/assessing-risk-bias-included-studies>). Selection bias refers to systematic differences between baseline characteristics of the groups that are compared. For example, emergency room (ER) patients are compared to surgical patients. The bias occurs when there are systematic differences in patient characteristics which are associated with group assignment. Performance bias refers to systematic differences between groups in the care that is provided or in exposure to factors other than the interventions of interest. This may include services other than the practice being tested that are provided to one group but not the other. Exclusion bias occurs when you have an exclusive sample but claim that the results have relevance for a more general population. Measurement bias refers to systematic differences between groups in how outcomes are determined. Changes in how outcomes are measured or recorded may change the sensitivity of the measure for detecting an outcome. If so, the study may document changes in outcome which reflect the sensitivity of the measure and not the true rate of occurrence.

D. Human subjects.

1. Patient population. Give as much information as possible about the group(s) you are selecting for the quality improvement study. Note that if there are any differences in patient mixes between those tested using the comparison practice and those tested using the alternative/intervention practice, bias may be introduced (see the discussion of selection/allocation bias above).
2. The age and gender of each subject should be recorded on the study intake form and reported as the age range and the percentages of male and female subjects.
3. IRB approval. Institutional review board (IRB) approval (or exemption) must be sought for any study before it has begun. Please consult with your relevant IRB official for appropriate procedures before beginning any study. LMBP welcomes the submission of unpublished QI data when the project is completed for inclusion in the next systematic review cycle (see

<http://www.cdc.gov/futurelabmedicine/about/default.aspx>).

- E. Facility description. Hospital size is the number of beds. For the type of facility, place a checkmark beside the type of hospital or private/reference laboratory where the QI study will be conducted.
- F. Study setting. Describe the setting(s) that will provide the patients or samples included in the study. For example, place a checkmark beside “ICU” (intensive care unit) if it will be the only nursing unit selected. If all hospitalized patients identified with a bloodstream infection will provide a larger sample, “Inpatient” would be the setting selected for the study. If your facility is designated a geriatric or cancer center but you select all hospitalized patients, then place a checkmark beside both.
- G. Sampling strategy for BSIs. The sample size is the number of patients/observations used for the usual (comparison) practice and the alternate (intervention) practice. Use the largest available sample at each time of measurement. For results to be reliable, the implemented practice should be the only difference in the study populations influencing the results. Describe your sample (tests, patient specimens, patients, or type of patient specimens) and the sample size. An example is 15,000 patient specimens tested for the usual (comparison) practice (prepractice) and 13,200 patient specimens tested for the alternate (intervention) practice (postpractice). In addition, list the organisms selected/included in the study. Note that a power analysis should be performed by a statistician prior to confirmation of the sample size. Statistical power is the probability of concluding that there is a difference when there is, in fact, a difference between your standard method and your new method (i.e., the probability that your study will detect a difference, given that one truly exists. An example of a nomogram for sample size calculation may be viewed in reference 81. Indicate the sampling category. Census sampling includes all eligible patients within a specified time period. Simple random sampling includes subjects (patients) selected for study inclusion by a formal random selection process in which each patient in the census is equally likely to be selected for participation in the study. Convenience sampling includes some subset of the census population because it is easy to access. For example, using data only from patient records that you can easily reach would be a convenience sample. For the “other” category, describe whether you are using a different sampling method. If you are using anything other than a census, simple random, or convenience sampling, you will likely need a sampling statistician to construct an appropriate sampling strategy.

QI Practice

- H. Alternate/intervention practice. Describe the testing practice that you will implement as an alternative (intervention) to the comparison (current) practice (described in section A1). Some examples include rapid molecular techniques (real-time PCR, PNA-FISH) and/or a variety of phenotypic techniques.
- I. Study dates. Prior to beginning the quality improvement study, it is recommended that you select dates for each

phase of the study. A pilot period for evaluating the implementation of a new practice and confirming its full implementation is often advisable. Assessing the effectiveness of a practice will be done once it is fully implemented and functioning as intended. Another consideration for study dates would be to inquire about other changes that may impact your data collection schedule or confound the results of your QI study. For example, it would be best to avoid times scheduled for a system-wide computer upgrade or other large-scale projects that might impact measurement or otherwise create bias. If a pilot phase is done prior to your QI project, indicate the start and end dates. If a pre/postimplementation study is selected as your QI design, indicate the start and end dates of each phase. Any other QI study design (see section C [QI study/design type]) selected by your facility may require multiple dates for a measurement of the practices included in the project. Additional information of project dates may be included on a separate page.

- J. Data collection. Are data collected as the study is being conducted (prospective), retrospectively (data taken from medical record charts), or both ways?
- K. Exclusions. List any data that are excluded from the study, such as duplicates or autopsy or other samples.
- L. Resource requirements/costs. Additional requirements and costs which are required to implement the practice should be listed. A full description of these adoptions and maintenance considerations should be included in the study write-up.

Outcome Measures

- M. Description of outcome measures. Options for outcome measures for your quality improvement study are listed below. A selection concerning the outcome measures should be finalized prior to the start of the study to ensure that the results will contribute to improved practices. Note the time that it took to report a rapid Gram stain result, another rapid test identification (PCR, FISH, etc.), a traditional identification, or a phenotypic result, the times of empirical (initial) therapy and targeted therapy, times when additional blood cultures were collected or additional laboratory or other tests were performed, and the lengths of hospital stays (days/hospital visit).
- N. Other possible measures. Additional information to enhance your project results, such as total costs for the usual (comparator) and alternate (intervention) practices, antibiotic costs (targeted and/or empirical), and other information could be selected for outcome measures. Note the average cost per hospital stay (or total cost per visit), the average cost of antibiotics per visit, the percent mortality, the percentage of patients showing antibiotic resistance, the percentage of patients with hospital-acquired infections, the acute physiology and chronic health evaluation (APACHE) score (a physiological assessment based on the degree of derangement of routinely measured physiological variables that includes the APACHE score and the simplified acute physiology score [SAPS]), the sepsis-related organ failure assessment (SOFA) score (organ-specific scoring, which is similar to therapeutic scoring with the

following underlying premise: the sicker a patient is, the more organ systems will be involved, ranging from organ dysfunction to failure), and any other possible measures taken (describe them).

- O. Recording method. Describe how the outcomes and test results will be recorded and data collected. Describe in the final write-up any deviation from the planned method. If there is a difference in the ways the usual (comparator) practice and the alternate (intervention) practice data are recorded, indicate the recording method for each practice with the specific outcome measure(s). Additional information may be included on a separate page.
- P. Statistical methods. List statistical methods to be used for the outcome measures. The basic descriptive analysis will include means, standard deviations, and confidence intervals. Additional statistical methods, such as odds ratio and risk ratio determinations, may require a statistician.

Results/Findings

- Q. Results/findings. Additional information in the QI project description of the patient population might include the diagnosis-related group (DRG) or the primary disease and comorbidities. After the quality improvement study has been completed, the next step will be to describe the findings of your study as they relate to the study design/outcome measures. For each studied outcome measure selected prior to the study, summarize the results/findings of the study/project as they relate to the practice implementation impact, i.e., the average time to the induction of targeted therapy, the LOS, the average time to report the rapid Gram stain result and/or other rapid tests, and the percent mortality. Provide the total number of observations upon which the results are based, the time period for observations, and the statistical tests performed. Discussion on whether the intervention improved outcomes relative to those of the comparator may be useful. Include calculations of the statistical significance of a difference between the measured outcomes listed in sections M and N of the usual (comparator) practice and of the alternate (intervention) practice.

Basic descriptive analysis, including sample size, should be reported for each outcome. If the data are continuous (e.g., time, amount, duration), data averages (means) and standard deviations should be provided along with confidence intervals (e.g., time measures). (The means and standard deviations can be calculated in Excel using the “ = average” and “ = stdev” functions. If continuous measures are highly skewed [e.g., most values are small with a few very large values], then reporting the median and range should be reported [use Excel “ = median” and range “ = min” and “ = max”].) With dichotomous measures (e.g., mortality), there should be a numerator (number of deaths/number discharged) and denominator (number of total patients in the study) for both pre- and poststudy practices. Include findings related to cost savings if that criterion was selected for your study.

Statistical assistance may be required for inferential tests of whether performance has changed significantly as a re-

sult of the alternate (intervention) practice. Additional space is available on the second page of the form (Fig. A2) for your results/findings.

Examples for pre/posttest findings follow.

- mean time to treat pretesting (comparator) = 20 min (SD = 5.5 min; $n = 175$); mean time to treat posttesting (intervention) = 12 min (SD = 3.5 min; $n = 180$);
- median LOS pretest (comparator) = 17.3 days (range, 3 to 40 days; $n = 1,600$); median LOS posttest (intervention) = 12 days (range, 2 to 27 days; $n = 1,250$);
- number of patients switched to targeted therapy pretest (comparator), 6 of 30 (20%); number of patients switched to targeted therapy posttest (intervention), 24 of 30 (80%);
- mean time to targeted therapy pretest (comparator) = 10 min (SD = 4.7 min; $n = 82$); mean time to targeted therapy posttest (intervention) = 4.5 min (SD = 1.4 min; $n = 74$).

R. Barriers to implementation. Describe any external activities occurring during the quality improvement project that may have influenced the results of the project, such as staff changes or new policy. Describe organizational, personnel, technical, etc., factors that inhibited or enhanced the adoption, implementation, and/or maintenance of the practice.

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