Impact of Infectious Diseases Consultation on the Outcome of Patients With Enterococcal Bacteremia: A Systematic Literature Review and Meta-analysis

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Background. Enterococcal bacteremia carries significant mortality. While multiple studies have evaluated the impact of infectious disease consultation (IDC) on this condition, these studies were limited by the low numbers of patients enrolled. This systemic literature review and meta-analysis was conducted to determine whether IDC is associated with a mortality benefit among patients with enterococcal bacteremia.

Methods. We performed a systematic literature search using 5 databases for studies evaluating IDC among patients with enterococcal bacteremia. We conducted a meta-analysis to assess whether IDC was associated with reduced mortality. Random-effects models were used to calculate pooled odds ratios (pORs). Heterogeneity was evaluated using I² estimation and the Cochran’s Q statistic test.

Results. The systematic literature review revealed 6496 reports, from which 18 studies were evaluated in the literature review and 16 studies in the meta-analysis. When all studies were pooled, the association between IDC and mortality was not statistically significant with a pOR of 0.81 (95% CI, 0.61–1.08) and substantial heterogeneity (I² = 58%). When the studies were limited to those reporting multivariate analysis including IDC, there was a significant protective effect of IDC (pOR, 0.40; 95% CI, 0.24–0.68) without heterogeneity (I² = 0%). Some studies also showed additional benefits to IDC, including appropriate antibiotic therapy and improved diagnostic use.

Conclusions. IDC was associated with 60% lower odds of mortality when patients were well-matched, potentially through improvement in the care of patients with enterococcal bacteremia. IDC should be considered part of routine care for patients with enterococcal bacteremia.

Keywords. enterococcal bacteremia; Enterococcus; infectious diseases consultation.

Enterococcus is a bacterial genus that is part of the commensal gastrointestinal microbiota [1] that can translocate across the intestine [2], causing bacteremia and other nosocomial infections [3]. Enterococcal bacteremia is associated with >20% mortality rates, especially with inappropriate antimicrobial therapy [4]. Most enterococcal infections are caused by Enterococcus faecalis or Enterococcus faecium. E. faecalis is typically ampicillin-susceptible and vancomycin-susceptible and is more frequently observed in community-acquired infections. E. faecium is highly associated with nosocomial infections and can often be a vancomycin-resistant Enterococcus (VRE); it is typically associated with worse outcomes [5, 6]. According to the 2015–2017 National Healthcare Safety Network data from the Centers for Disease Control and Prevention, Enterococcus species are the second most common antimicrobial-resistant pathogen implicated in all types of health care–associated infections, and the single most common cause of catheter-related bloodstream infections (CLABSI) in patients at long-term acute care hospitals (LTACHs) with most of these representing E. faecalis infections [7]. Longitudinal surveillance has shown stable rates of VRE bacteremia, accounting for 16% of bloodstream isolates since 2012 [8]. When compared with vancomycin-susceptible strains, VRE has been associated with a 2-fold increase in morbidity and mortality, likely related to differences in virulence [9, 10].

Enterococcal species have also been implicated as the causative pathogen in cases of infective endocarditis (IE); these infections are more frequently caused by E. faecalis, with an incidence of 13%–25% of patients presenting with E. faecalis bacteremia [9, 11]. One study found a 12% prevalence of IE in patients with enterococcal bacteremia, with in-hospital...
mortality of 15% and a 1-year mortality rate of 35% [11], while another study found a relapse rate of about 5% [12].

Infectious disease consultation (IDC) is often helpful for managing aspects of complicated infections including bacteremia and IE, such as identifying the primary source of infection and choosing an appropriate antimicrobial therapy. Studies have previously shown that IDC has been associated with improved rates of mortality in patients with bloodstream infections such as *Staphylococcus aureus* bacteremia [13–18] and candidemia [19], as well as other types of infections including cryptococcosis, compared with patients who did not receive IDC. There have been several studies evaluating the effect of IDC for patients with enterococcal bacteremia, but fewer studies compared with *S. aureus* bacteremia. These studies were also limited by the low numbers of patients enrolled. Whether there is a role for mandatory IDC in enterococcal bacteremia remains somewhat unclear. We conducted a systematic literature review and meta-analysis to determine whether IDC is associated with improved mortality among patients with enterococcal bacteremia.

**METHODS**

**Search Strategy and Selection Criteria for the Systematic Literature Review**

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [20] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [21]. The study protocol had been approved by the International Prospective Register for Systematic Reviews (PROSPERO) database (CRD42021266399). The systematic literature search was developed and performed by a health sciences librarian (R.J.S.). Search strategies using subject headings and keywords were created for PubMed (United States NIH), Embase (Elsevier), Web of Science – Core Collection (Clarivate), CINAHL (EBSCO), and Cochrane CENTRAL (Wiley). The searches were conducted on August 5, 2021, and updated on December 30, 2021, without any date limitations; the studies were not limited to only those published in English. All database results were exported to EndNote and de-duplicated (Supplementary Table 1) [22]. Inclusion criteria were as follows: (1) original research manuscripts (ie, randomized control trials, cross-sectional, case–control, and cohort studies) and (2) assessed the effect of IDC on mortality in patients with enterococcal bacteremia. Exclusion criteria included the following: (1) editorials and commentaries and (2) animal studies. All potentially relevant studies were divided and screened independently by 2 of the reviewers (J.T. and H.S.).

**Data Abstraction and Quality Assessment**

Three independent reviewers (J.T., T.K., and A.R.M.) abstracted data from the studies using a standardized abstraction form; 2 of these 3 reviewers analyzed each article, with 1 reviewer (J.T.) reviewing all articles. The following data were collected as available: study design, study period, population characteristics, source of enterococci, percentage of VRE, the proportion of echocardiograms performed, and mortality. Nine authors were contacted for additional information, and 3 were able to provide additional information regarding the number of patients who died with and without IDC [23–25]. Any discordance was mediated by a fourth independent reviewer (H.S.) who also reviewed all articles; after discussion, the consensus response was reported.

Each study was assessed with the Downs and Black scale to evaluate the risk of bias and quality (Supplementary Table 2) [26]. All questions were answered as intended except for question #27 regarding Power, which was changed to a yes/no answer with associated points. The reviewers performed the component quality analysis independently, reviewed any discrepancies, and came to a consensus after discussion as previously described.

**Statistical Analysis**

We used random-effects models with inverse variance weighting to calculate the pooled odds ratio (pOR) and 95% CI. We performed stratified analyses by study location, presence/absence of adjustment for confounders, type of outcome (30-day mortality, 90-day mortality, or in-hospital mortality), and quality of study. Heterogeneity was assessed using $I^2$ estimation and the Cochran’s Q statistic test. Publication bias was evaluated by visual inspection of funnel plots. All meta-analyses were conducted using the Cochrane Review Manager (Revman), version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark).

**RESULTS**

A flowchart summarizing the article selection process is shown in Figure 1. We initially identified 9804 articles from the database search; after the removal of duplicate articles, 6496 articles were identified. After screening by title and abstracts, 204 full-text articles were evaluated, including an additional 2 studies that were added after screening the references of the articles. A total of 18 articles were included for our systemic literature review [23–25, 27–41] (Table 1). Two articles [31, 38] were later excluded due to incomplete data for the meta-analysis, leaving 16 studies for the meta-analysis [23–25, 27–30, 32–37, 39–41].

**Study Characteristics**

Of the 18 included studies, 14 (78%) were retrospective cohort studies [24, 25, 27–30, 32, 33, 35–39, 41], 2 (11%) were prospective cohort studies [23, 40], and 2 (11%) were quasi-experimental studies [31, 34]. Thirteen (72%) were performed at a single academic center [23–25, 27, 30–34, 36–41], 1 study was performed at 2 academic centers [29], another
study was performed at 99 Veteran Affairs hospitals [28], and
the other study was performed at 2 community hospitals
[35]. Two were performed at the same academic center [24,
36]. Most of the studies were conducted in the United States
(12/18, 67%) [24, 28, 29, 31, 32, 34–39, 41], followed by Japan
(2/18, 11%) [25, 30], Germany (1/18, 6%) [23], Italy (1/18, 6%) [27],
Singapore (1/18, 6%) [33], and Austria (1/18, 6%) [40].

Most of the studies (94%) evaluated adult patients [23–25,
27–29, 31–41], with median ages ranging from 53.7 to 75 years,
though 1 (6%) evaluated pediatric patients, with a median age
of 9.3 months [30]. Enterococcus species identification was
available in 15 of the studies (83%) [23–25, 27–34, 36–41].
VRE was identified in 13 of the studies (72%) [24, 27–32, 34,
36–39, 41], and was solely studied in 6 (33%) of the studies
[28, 29, 34, 36, 38, 39]; most of the VRE identified was E. faeci-
um. The source of enterococcal bacteremia was described in 14
studies (78%) [23–25, 27, 30–35, 37, 39, 41]. Primary line-
associated bloodstream infection was the main source in 3 stud-
ies (17%) [30, 31, 41], intra-abdominal infections were the main
source in 6 studies (33%) [23, 25, 27, 32, 33, 37], and urinary
tract infections were the main source in 1 study (6%) [35].

Patients with identified IE due to Enterococcus species were

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram. Abbreviation: ID, infectious diseases.
### Table 1. Summary of the 18 Studies Included in the Systematic Review

| First Author/Publication Year/Location | Setting | Study Design | Adjustment for Confounders | Study Period | Characteristic of Included Patients | Source of Bacteria | Enterococcus Species | Antimicrobials Studied | Outcome | D&B Score |
|---------------------------------------|---------|--------------|----------------------------|--------------|--------------------------------------|-------------------|----------------------|----------------------|---------|----------|
| Bartolletti/2019/ Bologna, Italy [27]  | Single academic center | Quasi-experimental study | Cox proportional hazard regression (result of multivariate analysis not available) | 4 y          | Adult, mean age 70 y 20.9% community-acquired 10.3% ICU admission 20.1% DM 24.7% CKD 12.8% cirrhosis 23.1% immunocompromised 23.6% malignancy 7.3% solid organ transplant Excluded polymicrobial bacteremia | UTI 17.7% | E. faecalis 56% | E. faecium 35.1% | Evaluated appropriateness of therapy and use of combination therapy, with suggested dosages included | Post-study of alert system and structured IDC for enterococcal bacteremia; 30-d mortality was the primary outcome | 20 |
| Brit/2017/USA [28] 99 Veterans Affairs hospitals | Retrospective cohort study | None | Adult patients who had VRE bacteremia treated with either linezolid or daptomycin 32% ICU admission 51.8% CKD 9.5% cirrhosis 3.2% HIV 37.3% malignancy 3.2% transplant Enterococcus with resistance to both linezolid and daptomycin was excluded | 11 y        | UTI 11.6% IAI 4.4% Line-associated 10.8% SSTI 3.3% Endocarditis 6% Unknown 47% Multiple sites 14.9% | UTI 13% | E. faecalis 100% | VRE 100% | Linezolid and daptomycin | IDC was associated with decreased 30-d mortality (370/1335, 27.7%, for IDC vs 549/1444, 38.0%, for NIDC: RR, 0.86; P < .001). The trend is the same among the linezolid therapy group and daptomycin therapy group, but not in the linezolid-to-daptomycin group. | 21 |
| Cattaneo/2021/ Freiburg, Germany [23] | Single academic center | Prospective cohort study | Cox regression analysis | 3 y 1 mo | Adult, median age 69 y 26% DM 30% CKD 10% chronic liver disease 3% VOD 43% malignancy 13% severe immunosuppression 40% polymicrobial bacteremia 42% ICU admission | UTI 14% | E. faecalis 100% | VRE 0% | Ampicillin as definitive therapy | In multivariate Cox regression analysis, ID was not significantly protective for mortality or recurrence within 90 d (HR, 0.87; 95% CI, 0.46–1.68). IDC was significantly associated with follow-up blood culture (91% vs 56%; P < .001), early source control (89% vs 65%; P = .0025), echocardiography (84% vs 32% for the linezolid-to-daptomycin group, and adequate treatment duration (76% vs 43%; P = .001). | 21 |
| Erlandson/2008/ Nebraska, USA [29] 2 academic centers | Retrospective cohort study | None | 32.7% CKD 61.9% liver dysfunction 40.7% malignancy 55.8% transplant | 12 y 2 mo | UTI 11% | E. faecalis 0.9% | E. faecium 99.1% | VRE 100% | Linezolid and quinupristin-dalfopristin | Outcome was in-hospital mortality. IDC was associated with higher in-hospital mortality (OR, 2.96; 95% CI, 1.02–8.61; P < .05) but not selected in the multivariate model. | 15 |
| Furuichi/2018/Tokyo, Japan [30] | Single academic center | Retrospective cohort study | Multiple logistic regression | 14 y 9 mo | Pediatric, median age 9.3 mo 31% polymicrobial bacteremia 15% transplant | UTI 9% | E. faecalis 62% | E. faecium 30% | Penicillins, glycopeptides (e.g., vancomycin), and aminoglycosides | 30-d mortality was 8% (8/100) among those who got IDC vs 17% (9/52) among those who did not (OR, 0.42; 95% CI, 0.15–1.15; P = .11). Multivariate analysis showed an OR of 0.56 (95% CI, 0.16–1.71; P = .28). IDC was associated with appropriate empiric therapy and definitive therapy. Source of bacteremia was less likely unknown with IDC (9% IDC vs 19% NIDC). | 20 |
| Gray/2018/Virginia, USA [31] | Single academic center | Quasi-experimental study | None | 3 y 11 mo | Adult, mean age 60 y 73.6% central venous catheter 38.2% community-acquired 38.2% renal failure 15.5% cirrhosis | UTI 5.5% | E. faecalis 30.9% | E. faecium 69.1% | Penicillins, vancomycin, daptomycin, and linezolid | Relationship between IDC and mortality was not available. | 21 |
| First Author/Publication Year/Location | Setting | Study Design | Adjustment for Confounders | Study Period | Characteristic of Included Patients | Source of Bacteremia | Enterococcus Species | Antimicrobials Studied | Outcome | D&B Score |
|---------------------------------------|---------|--------------|---------------------------|-------------|-----------------------------------|---------------------|----------------------|----------------------|----------|------------|
| Jindai/2014/ Wisconsin, USA [32]      | Single academic center | Retrospective cohort study | None                       | 2 y 10 mo    | Adult, mean age 57.1 y 57.1% central venous catheter 13.2% community-acquired 24.3% polymicrobial bacteremia 31.6% DM 12.8% cirrhosis 42.9% malignancy 31.8% transplant | UTI 9.5% IA 27.5% Line-associated 18.5% | E. faecalis 39.7% E. faecium 56.6% Others 3.7% VRE 39.7% | Not reported | Outcome was in-hospital mortality. IDC was similarly made among those who survived 98(153, 56.2%) vs those who died (20/35, 57.1%; P=.92). As a secondary outcome, IDC was significantly associated with elimination of bacteremia in multivariate analysis (OR, 2.50; 95% CI, 1.32–4.72; P=.005). | 19 |
| Jumah/2018/ Singapore [33]           | Single academic center | Retrospective cohort study | Multiple logistic regression (result of multivariate analysis not available) | 6 y 5 mo     | Adult, median age 75 y 14% ICU admission 36.8% DM 10.5% cirrhosis 7% immunocompromised 31.8% malignancy Excluded polymicrobial bacteremia | UTI 22.8% IA 31.6% Line-associated 33% SSTI 5.3% Endocarditis 5.3% Unknown 24.6% | E. faecalis 36.8% E. faecium 56.1% Others 7% VRE 0% | Vancomycin with and without aminoglycosides | IDC was similarly done for patients who survived after 30 d (28/47, 59.6%) vs those who died within 30 d (8/10, 50%; P=.72). | 22 |
| Lee/2020/Alabama, USA [24]          | Single academic center | Retrospective cohort study | Multiple logistic regression | 1 y 6 mo     | Adult, median age 59 y 16% community-acquired 53% ICU admission 36% DM 28% CKD 9% cirrhosis 9% IVDU 26% immunocompromised 4% connective tissue disease 2% HIV 8% hematological malignancy 12% transplant | UTI 10% IA 14% Line-associated 21% SSTI 3% Endocarditis 8% Bone & joint 8% Others 7% Unknown 32% | E. faecalis 65% E. faecium 33% Others 2% VRE 33% | Evaluated appropriateness of therapy; regimen not discussed | 30-d mortality was 12% (16/131) among those who got IDC vs 27% (20/74) among NIDC (P=.007). IDC was a significant protective factor for 30-d mortality (aOR, 0.35; 95% CI, 0.16–0.76; P=.07). IDC was associated with increased likelihood of repeat blood cultures (aOR, 12.81), echocardiography (aOR, 2.45), appropriate antibiotic duration (aOR, 0.65), and decreased likelihood of unknown source of bacteremia (aOR, 0.31). | 21 |
| MacVane/2016/South Carolina, USA [34]| Single academic center | Quasi-experimental study | None                       | 5 y          | Adult, 33.8% community-acquired 20.6% polymicrobial bacteremia 38.2% ICU admission 35.3% DM 19.1% renal replacement therapy 5.9% liver disease 4.4% HIV 47.1% hematological malignancy | UTI 10.3% IA 26.5% Line-associated 19.1% SSTI 1.5% Unknown 42% | E. faecalis 7% E. faecium 93% VRE 100% | Vancomycin, daptomycin, and linezolid | Outcome was in-hospital mortality; 36.2% (174/477) of patients who got IDC died, and 23.8% (52/219) of patients who did not died (OR, 1.91; 95% CI, 1.01–3.57). | 20 |
| Malone/1986/Ohio, USA [38]          | 2 community hospitals | Retrospective cohort study | None                       | 4 y          | Adult, 36.4% community-acquired 38.2% polymicrobial bacteremia | UTI 23.6% IA 10.9% Line-associated | Not reported | Evaluated appropriateness of therapy and use of combination therapy, with regimens included | Unclear what time frame was used for mortality; 54.5% (122/227) of patients who got IDC died, and 36.4% (122/336) of | 15 |
| First Author/Publication Year/Location | Setting | Study Design | Adjustment for Confounders | Study Period | Characteristic of Included Patients | Source of Bacteremia | Enterococcus Species | Antimicrobials Studied | Outcome | D&B Score | Patients who did not die (OR, 2.1; 95% CI, 0.32–5.94). |
|---------------------------------------|---------|--------------|---------------------------|--------------|-------------------------------------|---------------------|---------------------|---------------------|----------------|----------|--------------------------------------------------|
| McKinnell/2011/Alabama, USA [36]      | Single academic center | Retrospective cohort study | Multiple logistic regression | 3 y, 7 mo | Adult patients with nosocomial VRE bacteremia Mean age 53.7 y 51% polymicrobial bacteremia 39% ICU admission 36% DM 49% CKD 23% liver disease 22% immunocompromised 3% HIV 30% hematological malignancy 16% transplant | Not reported | E. faecalis 3% E. faecium 97% VRE 100% | Linezolid and daptomycin | IDC was done for patients who survived after 30 d (2153, 18%) vs who died within 30 d (782, 9%); P = .008. Multivariate analysis showed that IDC had a non-significant trend toward being protective (OR, 0.4; 95% CI, 0.2–1.2; P = .06). | 21 |
| Mercuro/2020/Michigan, USA [37]      | Single academic center | Retrospective cohort study | None | 6 y, 2 mo | Adult patients with history of solid organ transplant Median age 61 y 75% central venous catheter 36.5% community-acquired 50% polymicrobial bacteremia | UTI 8% IAI 83% Unknown 8% | E. faecium 100% VRE 79% | Daptomycin with or without a beta-lactam, and linezolid | 30-d mortality was 23% (11/48) among those who got transplant IDC. No information about N IDC. Transplant IDC was not associated with mortality in bivariate analysis (OR, 0.3; 95% CI, 0.2–6.2). | 18 |
| Nakagawa/2018/Washington, USA [38]   | Single academic center | Retrospective cohort study | None | 3 y, 11 mo | Adult, 17.2% DM 10.9% CKD 21.9% cirrhosis 81.3% immunocompromised 1.8% HIV 71.9% malignancy 10.9% solid organ transplant | Not reported | VRE 100% | Daptomycin and linezolid | Relationship between IDC and mortality was not available. | 19 |
| Nakakura/2019/Osaka, Japan [25]      | Single academic center | Retrospective cohort study | None | 5 y, 11 mo | Adult with Enterococcus faecium bacteremia treated with vancomycin Median age 73 y 26.7% central venous catheter Excluded if received dialysis | UTI 11.1% IAI 11.1% Line-associated 8.9% Biliary tract 48.9% Unknown 20% | E. faecium 100% VRE 0% | Vancomycin | IDC was done for 63.6% of patients who survived after 30 d (2153, 18%) vs 50% of those who died within 30 d (782, 9%); P = .50. | 20 |
| Narayanan/2019/New Jersey, USA [39] | Single academic center | Retrospective cohort study | None | 4 y, 8 mo | Patients with VRE bacteremia treated with either linezolid or daptomycin 59.1% central venous catheter 16.1% community-acquired 28% ICU admission | IAI 17.2% Line-associated 28.9% Endocarditis 5.4% Unknown 45.2% | E. faecium 100% VRE 100% | Linezolid and daptomycin | Outcome was 14d in-hospital mortality. Mortality was 22.1% (13/60) among those who got IDC vs 14.3% (17/119) among those who did not (P = .029). | 20 |
| Valentin/2021/Graz, Austria [40]    | Single academic center | Prospective cohort study | None | 1 y | Not well described Patients after RAST followed by ID consultation were compared with a historical cohort | Not reported | E. faecalis or E. faecium 100% VRE 0% | Evaluated changes in therapy after IDC; specific regimens not discussed | 30-d mortality was 50% (5/10) among those who got RAST and IDC vs 27.7% (13/47) among those who did not. | 14 |

Single Multiple logistic 5 y | Adult with hospital-onset UTI 10.5% | E. faecalis 53.2% | Evaluated appropriateness | IDC within 24 h after blood culture was done | 21 |
for 50% of patients who survived after 30 d (22/44) vs 52.1% of those who died within 30 d (76/146; \( P = .81 \)). IDC was associated with shorter time to appropriate therapy (adjusted risk ratio, 0.41; 95% CI, 0.26–0.64; \( P = .001 \)). Two studies [23, 30] reported increased elimination of bacteremia [32].

**Meta-analysis**

Sixteen studies were included in the meta-analysis [23–25, 27–30, 32–37, 39–41]. The between-study heterogeneity differed depending on the outcome assessed. When all 16 studies were included, studies were substantially heterogeneous, and there was not a statistically significant association between IDC and overall mortality (pOR, 0.81; 95% CI, 0.61–1.08; \( I^2 = 58\% \) (Figure 2). When the 3 studies that reported the multivariate analysis results were pooled, studies were homogeneous, and there was a significant protective effect of IDC (pOR, 0.40; 95% CI, 0.24–0.68; \( I^2 = 0\% \)) (Figure 3). For the 10 studies that used 30-day mortality as an outcome, IDC was significantly protective, but there remained substantial heterogeneity (pOR, 0.61; 95% CI, 0.43–0.88; \( I^2 = 65\% \)) (Figure 4A). For the 5 studies that exclusively evaluated VRE bacteremia, there was no association between IDC and mortality (pOR, 1.07; 95% CI, 0.58–1.98; \( I^2 = 60\% \) (Figure 4B). For the 12 retrospective cohort studies included in the meta-analysis, there was also no association between IDC and mortality (pOR, 0.81; 95% CI, 0.59–1.10; \( I^2 = 42\% \) (Supplementary Figure 1A). For the 12 studies with a Downs and Black score \( \geq 19 \), there was a significant protective association between IDC and mortality, with significant heterogeneity (pOR, 0.70; 95% CI, 0.52–0.93; \( I^2 = 54\% \) (Supplementary Figure 1B).

**Publication Bias**

The funnel plot (Supplementary Figure 2) revealed that the studies were reasonably balanced around the pORs. Thus, there was little evidence of publication bias.
DISCUSSION

When we pooled all 16 studies together from our systematic literature review and meta-analysis, we did not identify a statistically significant effect of IDC on overall mortality. However, when the studies were limited to only those that reported the result of multivariate analysis, there was a statistically significant protective association between IDC and mortality. Stratified analyses suggested a protective effect of IDC although some heterogeneity remained. Some studies also showed additional benefits to IDC, including a shorter time to appropriate antibiotic therapy, appropriate duration of antibiotic use, increased diagnostic use such as repeat blood cultures or echocardiography, and better source identification.

There was noted to be marked heterogeneity in the included studies. An explanation for the lack of statistical significance and presence of heterogeneity when all 16 studies were included in the meta-analysis could be the retrospective nature of these studies, as many of them were observational studies or pre–post studies. It may have been that these patients were not well-matched, such as more severely ill patients having received IDC vs those who were not as ill. When limited to studies that evaluated 30-day mortality, there was a statistically significant impact on mortality; however, there remained a degree of heterogeneity among the studies included.

When the meta-analysis was limited to studies that performed multivariate analysis including adjustment for patients receiving IDC compared with patients who did not receive IDC [24, 30, 36], the association between IDC and mortality became significantly more protective with a 60% reduction in mortality. There was also greater homogeneity noted among these 3 studies. This result aligns with the benefit of IDC in patients with S. aureus bacteremia [13–18]. These studies have suggested increases in quality of care and decreases in treatment failure, mortality, and hospital length of stay. Like S. aureus bacteremia, enterococcal bacteremia is highly associated with IE and significant mortality [11]. ID physicians can assist in choosing appropriate antimicrobial therapy in a timely manner, which is associated with improved outcomes [41]. Patients with IDC have more blood cultures drawn, leading to a more accurate assessment of bacteremia clearance [23, 32]. ID physicians are often able to elucidate the likely primary source of infection and recommend appropriate workup for potential complications, including higher rates of central line removal [24] and other early source control [23]. IDC is also associated with higher rates of obtaining echocardiography, an increase in appropriate antibiotic duration based on the primary source of infection, and increased surgical interventions [23, 24]. Identification of IE in patients with enterococcal bacteremia is very important, as prolonged combination antibiotic therapy, rather than monotherapy, is recommended by the guidelines for the treatment of enterococcal IE to achieve a better outcome [42, 43]. We believe that such improvements in the quality of care for patients with enterococcal bacteremia may lead to improved outcomes for those patients.

When assessing the association between IDC and mortality in patients with VRE bacteremia, there does not appear to be an improvement in patients who receive IDC. The exact reason for not seeing the benefits of IDC in patients with VRE bacteremia is not clear. Among the 6 studies included in the systematic review that exclusively evaluated patients with VRE bacteremia, 2 studies reported improved outcomes with IDC.

**Figure 2.** All 16 studies included in the meta-analysis. Abbreviations: IDC, infectious disease consultation; IV, inverse variance.
[28, 36], 1 study reported worse outcomes with IDC [29], and 3 did not find any significant difference [34, 38, 39]. Britt et al. reported in their study involving 2779 patients in 99 Veterans Affairs health care systems that IDC was associated with a significantly lower 30-day mortality (27.7% in IDC vs 38.0% in no IDC; \( P < .001 \)). The protective effect was observed among patients treated with daptomycin, linezolid, or sequential treatment with linezolid to daptomycin [28]. Unfortunately, detailed information was not available in the other studies. It is possible that a protective effect was not observed due to the heterogeneity among studies. Perhaps unfamiliarity with therapeutic options beyond vancomycin in patients with VRE is more likely to prompt IDC, but any potential benefit is limited by the smaller number of available effective antimicrobials. It is likely that a diagnosis of VRE bacteremia is more likely to prompt an IDC compared with a diagnosis of E. faecalis bacteremia, especially if there is a lack of knowledge regarding the association of E. faecalis bacteremia with IE and without routine echocardiography which may not occur without IDC [42]. Around 25% of patients with enterococcal bacteremia undergo routine echocardiography [43], likely leading to underdiagnosis of IE in these patients. A prospective study showed that

![Figure 3](image_url)

**Figure 3.** Studies using multivariate analysis with results available. Abbreviations: IDC, infectious disease consultation; IV, inverse variance.

![Figure 4](image_url)

**Figure 4.** Stratiﬁed analysis with studies using 30-day mortality as an outcome (A) and studies exclusively evaluating VRE bacteremia (B). Abbreviations: IDC, infectious disease consultation; IV, inverse variance; NIDC, no infectious disease consultation.
routine echocardiography done on consecutive patients diagnosed with *E. faecalis* bacteremia was associated with a concurrent diagnosis of IE in 26% of patients after discussion with an endocarditis team [44]. Patients with enterococcal IE may also be more prone to poorer outcomes compared with patients with enterococcal bacteremia without IE, regardless of IDC.

Our systematic literature review and meta-analysis have several limitations. First, all the studies included in our meta-analysis were either cohort studies or quasi-experimental pre–post studies, and 2 were performed at the same academic center. In addition, most of the included studies did not aim to compare patients who received IDC with those who did not. Although our stratified analysis which used the 3 studies with multivariate analysis results suggested a protective effect of IDC after confounders were adjusted, there is still a risk for residual confounders which could not have been adjusted. Furthermore, most of the included studies did not evaluate IDC as a time-dependent variable; therefore, there may be an implicit survival bias in patients who lived long enough to receive IDC (immortal bias). Second, we did not include 4 studies that conducted multivariate analysis but did not report their results in our stratified analysis. It is possible that the presence of IDC was not selected in their final model due to the lack of a strong association with mortality, and therefore was not reported. In that case, it is possible that the estimate of a 60% reduction in the association between IDC and mortality was overestimated. Third, some of the included studies did not have well-matched data. When we used meta-analysis with inverse variance weighting, the results of these studies were modified to a normal distribution. Nevertheless, we believe this effect was minimal and did not affect the overall interpretation of our results. Finally, our meta-analysis did not evaluate the rates of empiric appropriate antibiotic use, nor obtain repeat blood cultures or echocardiograms in patients who received IDC compared with those who did not due to the limited number of studies. We also did not evaluate the effect of IDC on hospital length of stay or other costbenefit analyses. Such subanalyses might further elicit a benefit of IDC and would likely merit further research.

In conclusion, our meta-analysis did not observe a significant decrease in mortality in patients with enterococcal bacteremia who received IDC. However, the association between IDC and improved mortality outcomes was more apparent when analyzing studies adjusting for important confounders. There also did not appear to be a significant association between IDC and improved mortality in patients with VRE bacteremia. IDC confers additional benefits in improving quality of care, such as shorter time to appropriate antibiotic therapy, appropriate duration of antibiotic use, and increased diagnostic use such as repeat blood cultures or echocardiography, which results in better source identification, suggesting a role for IDC even without an apparent mortality benefit. Although this meta-analysis’s results need to be validated by a well-designed large-scale study, we believe our study highlights another condition in which IDC should be considered a part of the standard of care.

**Supplementary Data**

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

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**Patient consent.** As a systematic literature review and meta-analysis, our study did not include factors necessitating patient consent.

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