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Follow-Up Blood Cultures in Streptococcal and Enterococcal Bacteremia: A Systematic Review of Persistent Bacteremia and Its Clinical Significance

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Abstract

Follow-up blood cultures are frequently obtained after streptococcal or enterococcal bloodstream infection, although their clinical value remains uncertain. This systematic review evaluated the frequency, predictors, and clinical significance of persistent bacteremia among adults undergoing repeat blood culture sampling. MEDLINE via PubMed, Embase, Scopus, and Web of Science Core Collection were searched from inception through February 28, 2026. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Eligible observational studies reported follow-up culture findings, predictors of persistence, clinical outcomes, or management consequences. Six studies comprising 1,668 participants were included: five retrospective studies and one prospective multicenter cohort. Findings were synthesized narratively because of clinical and methodological heterogeneity. Reported persistent bacteremia or positive follow-up culture frequencies ranged from 3.2% to 22.2%, with important differences in definitions, sampling intervals, and antimicrobial exposure. Streptococcal persistence varied by species and was associated with endocarditis and other deep-seated infections. Enterococcal persistence was associated with endocarditis, hematologic malignancy, severe neutropenia, positivity of all index culture bottles, and inadequate source control. In the prospective VENOUS I cohort, microbiological failure occurred in 16.8% and independently predicted in-hospital mortality (adjusted hazard ratio 2.40, 95% confidence interval 1.34-4.31), whereas mortality associations in other cohorts were inconsistent or imprecise. Some studies reported longer treatment, hospitalization, or greater relapse among persistently positive patients; evidence documenting direct management changes was limited. Quality in Prognosis Studies assessment classified four studies as having moderate overall risk of bias and two as high risk, principally reflecting selection, confounding, and analytical limitations. Persistent positivity may identify patients at increased clinical risk, but these associations do not establish whether routine or selective sampling improves outcomes or whether omitting cultures is safe. A risk-adapted testing strategy remains a hypothesis requiring prospective validation.

Categories: Other, Hematology, Internal Medicine
Keywords: bloodstream infection, diagnostic stewardship, enterococcal bacteremia, follow-up blood cultures, infective endocarditis, persistent bacteremia, source control, streptococcal bacteremia

Introduction And Background

Blood cultures are central to identifying the causative organism, determining antimicrobial susceptibility, and guiding treatment in bloodstream infection. Infection complicated by organ dysfunction constitutes sepsis and requires timely recognition and management [1]. Sepsis guidance supports obtaining appropriate microbiological cultures before antimicrobial administration when this does not materially delay treatment [2]. Once bacteremia is documented, however, the value of repeating cultures is less certain. Culture yield depends on blood volume, the number of sets collected, antimicrobial exposure, collection timing, and contamination risk [3].

Follow-up blood cultures may document clearance or identify persistent bacteremia, broadly understood as continued recovery of the same organism from blood after the initial positive culture. Definitions vary: positivity more than 24 hours after the index culture is not clinically equivalent to continued positivity after several days of active antimicrobial treatment. The former may reflect early bloodstream clearance dynamics, whereas the latter raises greater concern about an unresolved focus or inadequate treatment response. Persistent positivity may signal infective endocarditis, an undrained abscess, infected prosthetic material, a retained intravascular device, or another deep-seated infection. Conversely, indiscriminate repeat sampling may increase phlebotomy, contamination, laboratory workload, and potentially

unnecessary antimicrobial exposure. Diagnostic stewardship literature supports selective blood culture use, although evidence establishing the effectiveness and safety of specific follow-up strategies remains incomplete [4,5]. Microbiological yield, prognostic significance, and actionable clinical value must therefore be distinguished: a positive result may identify increased risk without demonstrating that obtaining the culture improves outcomes.

The probability and clinical significance of persistence vary across organisms and clinical settings. Streptococcal species differ in their association with endocarditis, abscess formation, and sustained bloodstream seeding. A large observational study demonstrated substantial species-level variation in endocarditis prevalence among patients with streptococcal bloodstream infection, supporting organism-specific risk assessment [6]. Enterococcal persistence may reflect endocarditis, biofilm-associated infection, retained devices, inadequate source control, immunosuppression, or limited antimicrobial options, particularly with resistant isolates [7]. These differences provide a rationale for examining organism, host, and infection-source characteristics when interpreting follow-up culture findings. They do not, however, establish when repeat sampling can safely be omitted.

This systematic review evaluated the frequency, predictors, and clinical significance of persistent bacteremia among adults with streptococcal or enterococcal bloodstream infection who underwent repeat culture sampling. Outcomes included deep-seated infection, mortality, relapse or recurrence, hospitalization, antimicrobial treatment duration, and documented changes in clinical management. By separating microbiological yield from prognostic associations and management consequences, the review sought to identify potentially informative clinical features and evidence gaps relevant to the future evaluation of risk-adapted follow-up culture strategies.

Review

Materials and methods

Study Design and Reporting Framework

This systematic review examined the clinical value of follow-up blood cultures in adults with streptococcal or enterococcal bloodstream infection, with particular emphasis on the predictors and clinical consequences of persistent bacteremia. A review protocol was developed before formal study selection but was not prospectively registered. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The study-selection process was documented in a PRISMA flow diagram [8].

Review Question and PICO Framework

The review question was structured using a population, index prognostic factor, comparator, and outcomes framework adapted from PICO. The population comprised hospitalized adults aged 18 years or older with bloodstream infection caused by *Streptococcus* or *Enterococcus* species. The index prognostic factor was persistent positivity in one or more follow-up blood cultures obtained after the initial positive culture. The comparator comprised patients whose follow-up cultures were negative or whose bacteremia cleared within the persistence threshold defined by the individual study. Outcomes of interest included the frequency of persistent bacteremia; organism-related, host-related, microbiological, and source-related predictors of persistence; deep-seated or endovascular infection; mortality; infection relapse or recurrence; length of hospitalization; duration of antimicrobial therapy; and changes in diagnostic or therapeutic management attributable to follow-up culture results.

Information Sources and Search Period

MEDLINE via PubMed, Embase, Scopus, and Web of Science Core Collection were searched from database inception through February 28, 2026. The reference lists of included articles and relevant reviews were examined manually, and forward-citation searching was performed to identify eligible studies not retrieved through the electronic search. When multiple reports described overlapping populations, the most complete or methodologically informative report was retained; companion publications were used only to supplement missing information.

Search Strategy

The search strategy combined controlled vocabulary, including Medical Subject Headings and Emtree terms, with free-text keywords. The principal concepts were bloodstream infection, causative organism, follow-up blood cultures, and persistent bacteremia. A representative PubMed search was: ("Bacteremia"[MeSH] OR bacteremia OR bacteraemia OR "bloodstream infection*" OR "blood stream infection*") AND (Streptococcus OR streptococcal OR streptococci OR Enterococcus OR enterococcal OR enterococci OR VRE OR "vancomycin-resistant enterococc*") AND ("follow-up blood culture*" OR "repeat blood culture*" OR "subsequent blood culture*" OR "persistent bacteremia" OR "persistent bacteraemia" OR "bloodstream

clearance"). Additional terms included endocarditis, osteomyelitis, source control, risk factor*, predictor*, mortality, and relapse. Boolean operators, phrase searching, truncation, and database-specific subject headings were adapted for each platform. No organism-level restrictions were applied beyond streptococci and enterococci, allowing retrieval of species-specific and mixed-species studies. The complete search strategy can be found in the Appendix.

Eligibility Criteria

Peer-reviewed observational cohort, case-control, and cross-sectional studies involving adults with microbiologically confirmed streptococcal or enterococcal bloodstream infection were eligible. Studies were required to report follow-up blood culture testing and at least one relevant quantitative outcome, including the frequency of persistent positivity, predictors of persistence, associations with deep-seated infection or clinical outcomes, or changes in management attributable to follow-up culture results. Studies in which follow-up cultures were obtained from all participants and those in which testing was performed according to clinical judgment were eligible because both designs provided evidence regarding real-world diagnostic yield and risk stratification. Studies containing mixed bacterial populations were included only when findings for *Streptococcus* or *Enterococcus* species could be extracted separately.

The definition and timing of persistent bacteremia were accepted as specified by each study, provided that persistence represented recovery of the same organism after the index culture. This criterion permitted the inclusion of studies defining persistence as positivity more than 24 hours after the index culture, after at least 72 hours of active antimicrobial treatment, or after four or more days of directed therapy. These thresholds were not considered clinically equivalent and were extracted as a source of methodological heterogeneity. Both vancomycin-susceptible and vancomycin-resistant enterococcal infections were eligible, as were different streptococcal species, because organism-level variation was central to the review question.

Studies limited to pediatric populations, case reports, small case series without comparative or prognostic analyses, conference abstracts with insufficient methodological information, narrative or systematic reviews, editorials, laboratory-only investigations, and reports without original patient-level clinical data were excluded. Studies addressing *Staphylococcus aureus*, Gram-negative bacteria, fungi, or other ineligible pathogens exclusively were also excluded. Reports were ineligible if they did not distinguish persistent infection from contamination, did not report follow-up culture findings, or did not provide separately extractable streptococcal or enterococcal data. Studies were not excluded solely because persistent bacteremia was uncommon, as a low positivity rate remained relevant to the evaluation of diagnostic yield and stewardship.

Study Selection

Records were imported into reference-management software, and duplicate citations were removed before screening. Two reviewers independently screened titles and abstracts against the prespecified eligibility criteria. Potentially relevant articles underwent independent full-text evaluation by the same reviewers. Disagreements were resolved through discussion, with consultation with a third reviewer if consensus could not be reached. Reasons for excluding articles at the full-text stage were documented.

Data Extraction

Two reviewers independently used a standardized, pilot-tested extraction form. Extracted information included publication year, country, clinical setting, study design, recruitment period, sample size, eligibility criteria, patient characteristics, causative species, antimicrobial-resistance phenotype, timing and frequency of follow-up cultures, definition of persistence, initial antimicrobial therapy, source-control status, and the number or proportion of positive index-culture bottles. Data were also collected on endocarditis, osteomyelitis, discitis, epidural abscess, other deep-seated infections, hematologic malignancy, neutropenia, mortality, relapse, recurrence, length of stay, antimicrobial duration, and culture-related changes in diagnosis or management. Unadjusted and adjusted estimates, including odds ratios, hazard ratios, 95% confidence intervals, and corresponding P values, were extracted where reported.

Risk-of-Bias Assessment

Two reviewers independently assessed methodological quality using the Quality in Prognosis Studies (QUIPS) tool, which is appropriate for studies examining predictors and prognostic associations [9]. The assessment covered study participation, study attrition, prognostic-factor measurement, outcome measurement, control of confounding, and statistical analysis and reporting. Each domain was judged as having low, moderate, or high risk of bias and was supported by a brief justification. Particular attention was given to clinician-selected follow-up culture ordering, exclusion of patients without repeat cultures, survival to the time of repeat sampling, inconsistent persistence thresholds, small numbers of persistent events, confounding by indication, and differential investigation for deep-seated infection. Disagreements were resolved through discussion or third-reviewer adjudication. Risk-of-bias judgments informed the

interpretation of findings and were not converted into a numerical quality score.

Data Synthesis

Study characteristics and findings were summarized in structured evidence tables. Because the included studies differed substantially in organism distribution, follow-up culture timing, persistence definitions, patient populations, antimicrobial exposure, and outcome measurement, the principal synthesis was narrative. Results were organized by organism group, persistence frequency, deep-seated infection, source control, host vulnerability, initial bloodstream burden, treatment-related factors, clinical outcomes, and actionable yield. Streptococcal and enterococcal studies were considered separately before areas of convergence were examined.

Results

Study Selection

The systematic search identified 455 records: 112 from MEDLINE via PubMed, 146 from Embase, 104 from Scopus, and 93 from Web of Science Core Collection. After removal of 29 duplicates, 426 records underwent title and abstract screening, and 311 were excluded. Of 115 reports sought for full-text retrieval, 12 could not be retrieved, leaving 103 reports for eligibility assessment. Ninety-seven reports were excluded for prespecified reasons, most commonly ineligible pathogens, absence of follow-up blood-culture findings, or lack of separately extractable streptococcal or enterococcal data. Six studies were included, comprising 1,668 analyzed participants, of whom 1,446 underwent follow-up blood culture sampling. The study-selection process and reasons for full-text exclusion are presented in Figure *1*.

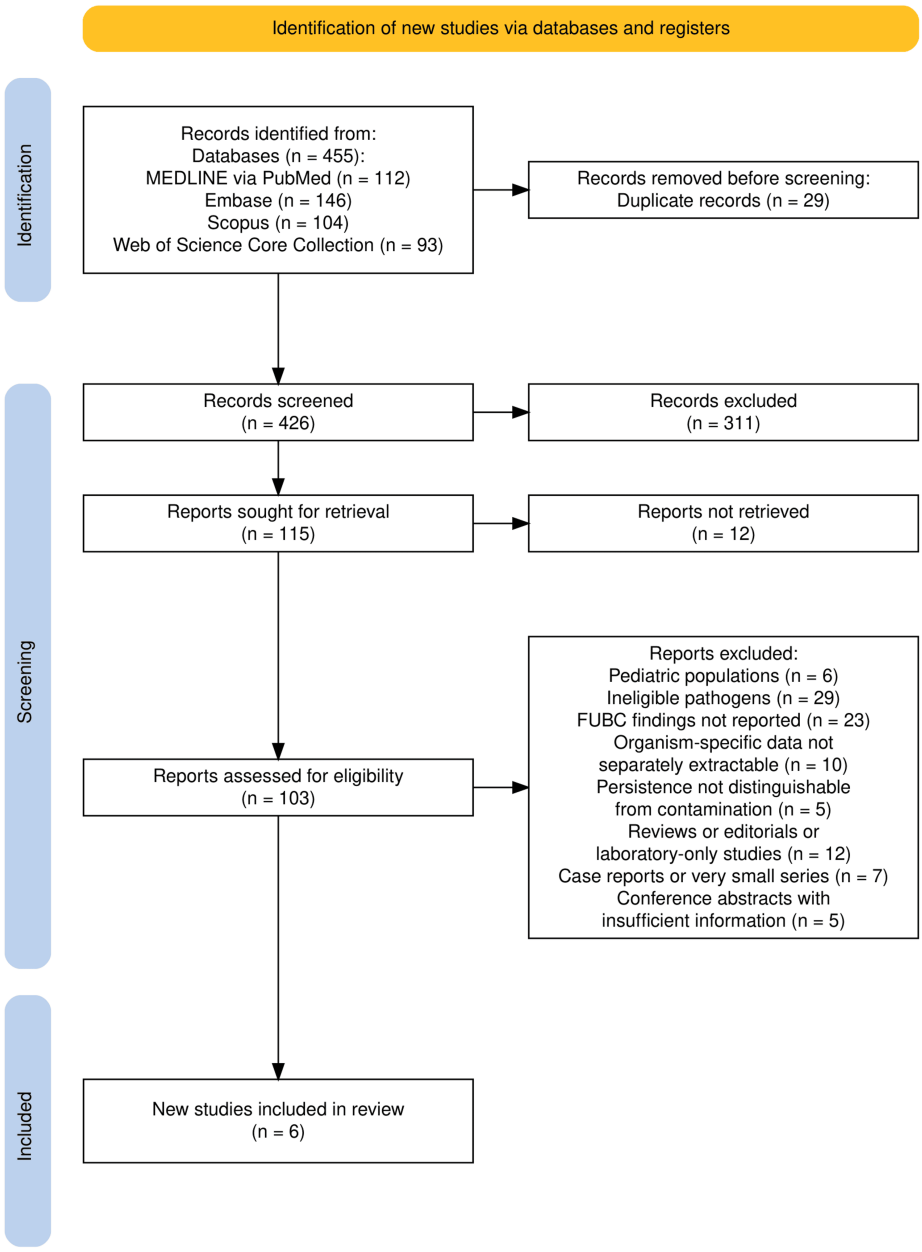


FIGURE 1: PRISMA flow diagram of study identification, screening, eligibility assessment, and inclusion.

Abbreviations: MEDLINE, Medical Literature Analysis and Retrieval System Online; n, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Characteristics of the Selected Studies

Six observational studies comprising 1,668 analyzed participants were included: five retrospective studies and one prospective multicenter cohort. Of these participants, 1,446 underwent follow-up blood culture sampling. Recruitment periods spanned 2011 to 2024 across the United States, the Netherlands, Italy, and Spain. Using mutually exclusive organism categories, two studies included exclusively streptococcal bacteremia, three included exclusively enterococcal bacteremia (including one restricted to vancomycin-resistant enterococci), and one included both streptococcal and enterococcal cases. Analyzed cohort sizes ranged from 108 to 454 participants, and reported persistent bacteremia or positive follow-up culture frequencies ranged from 3.2% to 22.2%. Persistence definitions varied, including positivity more than 24 hours after the index culture, recovery of the same organism after at least 72 hours of appropriate therapy, lack of clearance ⩾4 days after the index culture, or continued positivity for ⩾4 days despite directed therapy. De Boer et al. reported follow-up culture positivity without a clearly established persistence threshold in the available report excerpt; these findings were distinguished from treatment-defined persistence. Detailed

study characteristics and principal findings are presented in Table 1.

Study; country	Design; population	Organism(s)	Follow-up culture and persistence definition	Persistent bacteremia or positive FUBC; key predictors	Deep-seated infection and clinical outcomes
de Boer et al., 2026; Netherlands [10]	Single-center retrospective observational cohort, 2016–2021; 458 patients initially identified and 316 analyzed: 205 streptococcal and 111 enterococcal cases	*Streptococcus* spp.; *Enterococcus* spp.	FUBC obtained in 94/316 (29.7%): 57/205 (27.8%) streptococcal and 37/111 (33.3%) enterococcal cases. Sampling interval, explicit same-organism requirement, and persistence threshold relative to active therapy were not specified in the available report excerpt	Positive FUBC in 7/57 (12.3%) streptococcal and 8/37 (21.6%) enterococcal cases; predictors NR. These estimates describe reported FUBC positivity rather than persistence after a defined period of active treatment	Positive FUBC rarely led to alternative diagnoses and did not change antibiotic selection; treatment duration was prolonged in 1/15 positive cases. No association with ICU admission, mortality, or longer hospitalization was reported
Tuma et al., 2026; USA [11]	Multisite retrospective cohort, 2023–2024; 454 hospitalized adults with monomicrobial streptococcal bacteremia and FUBC	*Streptococcus* spp., analyzed by species group	FUBC collected >24 h after the index culture during active therapy; recovery of the same organism represented persistence	Positive FUBC in 48/454 (10.6%); positivity ranged from 0% for *S. pyogenes* to 18.5% for the *S. anginosus* group. *S. anginosus* independently predicted positivity (aOR 3.28, 95% CI 1.28–8.38)	Positive versus negative FUBC was associated with endocarditis (22.9% vs 12.1%; P=.04), osteomyelitis (16.7% vs 5.4%; P=.005), relapse (8.5% vs 2.7%; P=.047), and longer antibiotic treatment (30 vs 16 days; P=.01), but not mortality, length of stay, or infection-related readmission
Siegrist et al., 2020; USA [12]	Single-center retrospective cohort, 2013–2018; 314 adults with monomicrobial streptococcal bacteremia and ≥1 FUBC	*Streptococcus* spp.	Positive FUBC defined as recovery of the same streptococcal species >24 h after the index culture during active therapy	Persistent bacteremia in 10/314 (3.2%); contaminants in four (1.3%) and a new pathogen in three (1.0%). Deep-seated or endovascular infection characterized most positive cases	Positive versus negative FUBC was associated with endocarditis (50.0% vs 11.5%), epidural abscess (20.0% vs 1.3%), and discitis/vertebral osteomyelitis (30.0% vs 4.6%). Positive cases had longer hospitalization (12.9 vs 7.1 days; P=.004) and antibiotic treatment (P=.03); mortality was not increased
Bussini et al., 2022; Italy and Spain [13]	International two-center retrospective cohort, 2011–2019; 244 hospitalized adults with monomicrobial enterococcal bacteremia and FUBC	*Enterococcus* spp.	Persistence defined as recovery of the same *Enterococcus* species after ≥72 h of appropriate antibiotic therapy	Persistent bacteremia in 33/244 (13.5%). Independent predictors were hematologic malignancy (aOR 4.60, 95% CI 1.32–16.00), infective endocarditis (aOR 7.99, 95% CI 2.20–28.90), and initial daptomycin therapy (aOR 4.50, 95% CI 1.29–15.61)	Thirty-day mortality was higher with persistence (32% vs 18%), with poorer unadjusted survival (log-rank P=.002). The adjusted association with mortality did not reach statistical significance (adjusted HR 1.93, 95% CI 0.92–4.04; P=.08)
Fox et al., 2022; USA [14]	Single-center retrospective case-control study, 2016–2020; 108 adults with VRE bloodstream infection	Vancomycin-resistant *Enterococcus* spp.	Persistent bacteremia defined as bacteremia for ≥4 days despite VRE-directed therapy; controls had documented clearance within four days of active treatment initiation	Persistent bacteremia in 24/108 (22.2%). Adjusted associations were severe neutropenia (aOR 12.12, 95% CI 1.47–100.26), all four index-culture bottles positive (aOR 11.29, 95% CI 2.42–52.68), and lack of source control	Unadjusted comparisons showed numerically higher in-hospital mortality (58% vs 40%; P=.121), recurrence (17% vs 6%; P=.090), and breakthrough bacteremia (13% vs 7%; P=.402), without statistically significant differences

				(aOR 11.88, 95% CI 2.48–56.91)	
Contreras et al., 2022 (VENOUS I); USA [15]	Prospective multicenter observational cohort, September 2016–March 2018; 232 adults with enterococcal bloodstream infection across 11 hospitals, ≥1 FUBC within seven days, and an available index isolate	*Enterococcus faecalis*; *Enterococcus faecium*; 176 vancomycin-susceptible and 56 vancomycin-resistant infections	FUBC ordered by treating clinicians; microbiological failure defined as lack of bloodstream clearance ≥4 days after the index culture	Microbiological failure in 39/232 (16.8%): 27/176 (15.3%) vancomycin-susceptible and 12/56 (21.4%) vancomycin-resistant infections. Multivariable analyses evaluated predictors of mortality rather than predictors of persistence	Overall in-hospital mortality was 42/232 (18.1%). Microbiological failure independently predicted in-hospital mortality (adjusted HR 2.40, 95% CI 1.34–4.31; P=.003); in the *E. faecium* subgroup, the corresponding HR was 5.03

TABLE 1: Characteristics and principal findings of the included studies.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; FUBC, follow-up blood culture; h, hours; HR, hazard ratio; ICU, intensive care unit; NR, not reported; OR, odds ratio; S., *Streptococcus*; spp., species; USA, United States of America; VRE, vancomycin-resistant *Enterococcus*; vs, versus

Quality Assessment

Using the QUIPS tool, four studies were judged to have an overall moderate risk of bias and two a high risk, as summarized in Table *2*. Overall classifications reflected the domain-level pattern rather than a numerical score: high-risk studies combined high risk in confounding with high risk in participation or analysis/reporting, whereas moderate-risk studies had residual methodological concerns without high-risk domain judgments. De Boer et al. [10] had substantial concerns regarding selective repeat sampling and limited confounding control; Siegrist et al. [12] had limited adjustment and only 10 persistent events, constraining reliable comparative analyses. Tuma et al. [11] and Bussini et al. [13] were rated moderate because adjusted analyses reduced, but did not eliminate, selection and confounding concerns. Fox et al. [14] had concerns related to exclusion of early deaths, heterogeneous sampling, and imprecise estimates from a small number of persistent events. Contreras et al. [15] provided prospective data and adjusted mortality analyses, but selection requiring repeat cultures and an available isolate, variable sampling, and potential time-related bias remained concerns. Clinician-selected testing and exclusion of early deaths were considered under participation rather than attrition, because they affected entry into the analyzed cohorts. Differential investigation for deep-seated infection was considered under outcome measurement and confounding, while small event counts and potential time-related bias informed analysis/reporting judgments. Accordingly, associations were interpreted cautiously as prognostic signals rather than evidence that repeat testing itself improves outcomes.

Study	Participation	Attrition	Predictor measurement	Outcome measurement	Confounding	Analysis/reporting	Overall risk
de Boer et al., 2026; Netherlands [10]	High	Low	Moderate	Low	High	Moderate	High
Tuma et al., 2026; USA [11]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Siegrist et al., 2020; USA [12]	Moderate	Low	Low	Low	High	High	High
Bussini et al., 2022; Italy and Spain [13]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Fox et al., 2022; USA [14]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Contreras et al., 2022 (VENOUS I); USA [15]	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate

TABLE 2: Risk-of-bias assessment of the included studies using the Quality in Prognosis Studies tool.

QUIPS, Quality in Prognosis Studies; USA, United States of America.

Discussion

Principal Findings and Central Interpretation

Across the six included studies, persistent streptococcal and enterococcal bacteremia was not a uniform phenomenon, with reported frequencies ranging from 3.2% in the streptococcal cohort studied by Siegrist et al. [12] to 22% in the vancomycin-resistant enterococcal cohort evaluated by Fox et al. [14]. In the broader cohort examined by de Boer et al., positive follow-up cultures rarely led to an alternative diagnosis, altered antimicrobial selection, or predicted adverse clinical outcomes, suggesting limited value for indiscriminate repeat sampling [10]. However, Tuma et al. and Siegrist et al. found that persistent streptococcal positivity was concentrated among patients with endocarditis, osteomyelitis, vertebral infection, or epidural abscess [11,12]. Similarly, Bussini et al. and Fox et al. identified a higher-risk enterococcal phenotype characterized by hematologic malignancy, severe neutropenia, high initial culture burden, endocarditis, and inadequate source control [13,14]. Adding prospective evidence, Contreras et al. reported microbiological failure in 39 of 232 patients (16.8%) in VENOUS I, defined as lack of bloodstream clearance ⩾4 days after the index culture. Microbiological failure independently predicted in-hospital mortality (adjusted HR 2.40, 95% CI 1.34-4.31), supporting the prognostic significance of delayed enterococcal clearance [15]. These observations neither support universal repetition nor justify universal avoidance of follow-up cultures. Rather, they distinguish the prognostic importance of documented persistence from the unproven benefit of routine repeat sampling and suggest that follow-up cultures may provide clinically relevant information when used selectively in patients with features indicating sustained bloodstream seeding, impaired clearance, or an unresolved infectious focus.

Organism-Specific Heterogeneity in Persistent Bacteremia

The available evidence indicates that neither streptococcal nor enterococcal bacteremia should be regarded as a microbiologically homogeneous entity. Tuma et al. reported no positive follow-up cultures among patients with *Streptococcus pyogenes* bacteremia, relatively low positivity with *Streptococcus pneumoniae* and group C or G streptococci, and higher positivity among viridans-group streptococci and the *Streptococcus anginosus* group [11]. This variation is biologically plausible because viridans-group streptococci are established causes of infective endocarditis, whereas the *S. anginosus* group has a recognized propensity for abscess formation and anatomically concealed infection [16]. Persistent positivity may therefore reflect differences in tissue tropism and source accessibility rather than the severity of bloodstream infection alone. Enterococcal persistence occurred in 13.5% of patients studied by Bussini et al., 21.6% of tested enterococcal cases reported by de Boer et al., and 22% of patients with vancomycin-resistant *Enterococcus* (VRE) bacteremia evaluated by Fox et al. [10,13,14]. In VENOUS I, microbiological failure occurred in 15.3% of vancomycin-susceptible infections and 21.4% of vancomycin-resistant infections; these descriptive differences do not establish resistance as an independent determinant of persistence [15]. The observed frequencies may reflect the concentration of healthcare exposure, immunosuppression, antimicrobial resistance, biofilm-associated infection, retained devices, and incomplete source control within the studied enterococcal populations. Enterococcal tolerance to cell wall-active antimicrobial therapy and the frequent coexistence of complex host-related and source-related factors provide further biological support for delayed clearance [17]. Nevertheless, direct comparisons require caution because the studies differed in patient selection, resistance patterns, timing of follow-up cultures, and definitions of persistence. Species-specific findings were not consistently reported across studies, although VENOUS I identified a particularly strong association between microbiological failure and mortality in the *Enterococcus faecium* subgroup [15].

Persistent Positivity as a Signal of Deep-Seated Infection

Persistent bloodstream positivity may be understood as both a consequence and a potential marker of anatomically unresolved infection. Tuma et al. found that positive follow-up cultures were more frequent among patients with endocarditis and osteomyelitis [11], while Siegrist et al. observed higher frequencies of endocarditis, epidural abscess, and discitis or vertebral osteomyelitis among persistently positive cases [12]. In enterococcal bacteremia, Bussini et al. identified infective endocarditis as a strong independent correlate of persistence [13]. These associations are clinically plausible because infected valves, bone, epidural collections, and other poorly accessible or undrained foci may sustain bloodstream seeding despite active antimicrobial therapy. Contemporary endocarditis guidance similarly recognizes persistent bacteremia as an important feature of uncontrolled infection [18]. Nevertheless, the direction of these relationships cannot be reliably determined from the available observational evidence. Clinical suspicion of endocarditis or another deep focus may have prompted repeat cultures, whereas persistent positivity may subsequently have led to echocardiography or additional imaging, creating the potential for reverse causality and detection bias. Persistent positivity should therefore not be regarded as an independent diagnostic test for endocarditis. However, it may increase the pretest probability of an endovascular, osteoarticular, or otherwise deep-seated focus and support targeted diagnostic evaluation within the appropriate clinical context.

Source Control and Initial Bloodstream Burden

The findings of Fox et al. suggest that persistent bacteremia may function as a dynamic indicator of unresolved infection rather than solely as evidence of inadequate antimicrobial activity [14]. Lack of source

control was strongly associated with persistent VRE bacteremia, supporting the biological premise that an undrained abscess, retained infected catheter, infected cardiac or vascular device, prosthetic material, endocardial vegetation, or incompletely managed osteoarticular focus may sustain bloodstream seeding. This interpretation is consistent with contemporary sepsis guidance, which emphasizes timely identification and control of an anatomic source when infection cannot be eradicated with antimicrobial therapy alone [19]. Positivity of all four index culture bottles was also strongly associated with persistence in the study by Fox et al. [14], potentially indicating a greater circulating organism burden or continuous seeding from an endovascular or uncontrolled focus. However, the number of positive bottles is influenced by the volume of blood collected, the number and timing of culture sets, previous antimicrobial exposure, collection technique, and laboratory procedures. Bottle positivity should therefore be interpreted as a readily available risk marker rather than a standardized quantitative measure of bacterial burden. Taken together, these findings support using persistent positivity as a prompt to reassess source identification and source control, rather than merely as an indicator of whether the selected antimicrobial agent is microbiologically active.

Host Vulnerability and Treatment-Related Factors

Persistent bacteremia appears to arise from interactions among pathogen characteristics, host immune function, infection source, and treatment context. Bussini et al. identified hematologic malignancy as an independent correlate of persistent enterococcal bacteremia [13], while Fox et al. reported an association with severe neutropenia [14]. Impaired phagocytic clearance, mucosal disruption, repeated healthcare exposure, prolonged vascular access, antimicrobial resistance, and difficulty achieving source control may each contribute to delayed clearance in these populations. Enterococcal bloodstream infection has also been associated with adverse outcomes among patients with hematologic disease and recipients of hematopoietic cell transplantation [20]. Nevertheless, hematologic malignancy and neutropenia may function as causal contributors, markers of underlying illness severity, or modifiers of the consequences of persistent infection, and the available studies cannot fully distinguish among these roles. Bussini et al. also identified initial daptomycin therapy as a predictor of persistence [13], but this finding should not be interpreted as evidence that daptomycin itself promotes microbiological failure. Daptomycin may have been preferentially selected for resistant isolates, critically ill patients, suspected endovascular infection, previous treatment failure, or limited therapeutic alternatives, creating substantial potential for confounding by indication. Observational evidence further suggests that daptomycin exposure and dosage may influence outcomes in VRE bacteremia [21]. Species identification, antimicrobial susceptibility, administered dose, infection source, timing of active therapy, adequacy of source control, and host immune status should therefore be considered before persistence is attributed to a particular antimicrobial strategy.

Clinical Consequences and Actionable Yield

Interpretation of follow-up cultures requires a distinction among microbiological yield, prognostic association, and actionable yield. Microbiological yield refers to the proportion of follow-up cultures that remain positive, prognostic association concerns the relationship between persistence and subsequent outcomes, and actionable yield requires evidence that the result changed diagnostic evaluation, source control, or treatment. These dimensions were not consistently aligned across the included studies. de Boer et al. found that positive cultures rarely changed antimicrobial selection and prolonged treatment in only one patient [10]. In contrast, Tuma et al. reported associations between positivity, infection relapse, and longer antimicrobial treatment [11], while Siegrist et al. observed longer hospitalization and treatment among persistently positive cases [12]. In the enterococcal cohorts, Bussini et al. reported higher crude 30-day mortality, although the adjusted association did not reach statistical significance [13]. Fox et al. similarly found numerical increases in mortality, recurrence, and breakthrough bacteremia, but these comparisons were statistically inconclusive [14]. A positive culture may therefore provide prognostic information without necessarily producing an immediate management change. Conversely, longer treatment following persistent positivity should not automatically be classified as beneficial or harmful. It may represent appropriate management of newly recognized endocarditis or osteomyelitis, calculation of treatment duration from documented clearance, clinician caution without diagnostic reclassification, or potentially avoidable antimicrobial exposure. Diagnostic stewardship requires consideration of whether testing is likely to inform a clinical decision rather than consideration of positivity alone [22]. Future studies should report the precise sequence linking culture results to imaging, specialist consultation, source-control intervention, antimicrobial modification, or discharge planning.

A Risk-Adapted Approach to Follow-Up Cultures

The collective evidence supports a provisional risk-adapted approach rather than routine repetition for every streptococcal or enterococcal bloodstream infection. The expected yield appears lower among clinically improving patients with *S. pyogenes*, *S. pneumoniae*, *S. agalactiae*, or group C or G streptococcal bacteremia when active therapy has been initiated, the source is apparent and controlled, prosthetic intravascular material is absent, and there is no clinical suspicion of endocarditis, osteomyelitis, abscess, or another deep-seated focus [11,12]. Conversely, repeat sampling may be more informative in patients with viridans-group or *S. anginosus* group bacteremia, enterococcal bacteremia accompanied by endovascular concern, VRE infection, an unknown or uncontrolled source, retained intravascular or prosthetic material, hematologic malignancy, severe neutropenia, positivity in all or nearly all index culture bottles, persistent

hemodynamic instability, or failure to improve clinically [11,13,14]. This framework is consistent with broader principles of blood culture stewardship, which favor testing when the pretest probability of persistence and the potential for a management change are sufficient to justify the associated clinical and laboratory burden [22,23]. However, these features have not been integrated into or externally validated as a clinical prediction rule. They should therefore inform individualized clinical judgment rather than function as fixed criteria. The decision to obtain follow-up cultures should reflect both the probability that bacteremia has not cleared and the likelihood that documenting persistence will alter investigation, source control, treatment, or prognostic assessment.

Limitations and Research Priorities

The conclusions of this review are constrained by an exclusively observational evidence base in which follow-up cultures were generally obtained according to clinician judgment. Restricting analyses to patients who underwent repeat sampling may have preferentially selected those with greater illness severity, suspected endovascular infection, delayed clinical improvement, or an unresolved source. The exclusion of early deaths in some studies may also have introduced survivor bias. Definitions of persistence varied materially, ranging from recovery of the same organism more than 24 hours after the index culture to continued positivity after at least 72 hours of active therapy or four days of directed treatment. These thresholds represent different biological and clinical states and should not be regarded as interchangeable. Additional limitations included small numbers of persistent events, heterogeneous antimicrobial exposure, residual confounding, possible reverse causality between persistence and the diagnosis of deep-seated infection, limited species-specific enterococcal data, and uncertainty regarding whether follow-up testing itself improves clinical outcomes. Culture yield may also be influenced by blood volume, number of sets, sampling interval, collection technique, prior antimicrobial exposure, and laboratory processing, reinforcing the need for standardized methods [23,24]. Future prospective multicenter studies should use predefined sampling intervals, report individual species and resistance phenotypes, standardize evaluation for endocarditis and other deep-seated infections, and document whether culture results directly changed imaging, source control, antimicrobial management, or discharge decisions. Externally validated risk models and pragmatic comparisons of routine versus selective sampling would be particularly valuable.

Conclusions

The available evidence characterizes the frequency and clinical significance of persistent streptococcal and enterococcal bacteremia but does not establish whether routine or selective follow-up blood culture sampling improves outcomes or whether omitting repeat cultures is safe. Persistent positivity appears to identify a higher-risk clinical phenotype associated with deep-seated infection, impaired host defenses, high initial culture burden, or inadequate source control. However, comparisons between patients with positive and negative follow-up cultures cannot determine the effectiveness of the testing strategy itself. A risk-adapted approach targeting patients at increased risk of incomplete bloodstream clearance is therefore a hypothesis requiring prospective validation, including assessment of missed persistent infections, management changes, clinical outcomes, and testing burden.

Appendices

Table *3* presents the complete database-specific search strategies, including the supplementary search terms and methods used to identify additional studies.

Database or search component	Platform and search coverage	Search strategy or specification
MEDLINE via PubMed	NCBI PubMed; inception through February 28, 2026	("Bacteremia"[MeSH] OR bacteremia OR bacteraemia OR "bloodstream infection*" OR "blood stream infection*") AND (Streptococcus OR streptococcal OR streptococci OR Enterococcus OR enterococcal OR enterococci OR VRE OR "vancomycin-resistant enterococc*") AND ("follow-up blood culture*" OR "repeat blood culture*" OR "subsequent blood culture*" OR "persistent bacteremia" OR "persistent bacteraemia" OR "bloodstream clearance")
Embase	Embase.com syntax; inception through February 28, 2026	('bacteremia'/exp OR bacteremia:ti,ab,kw OR bacteraemia:ti,ab,kw OR 'bloodstream infection*':ti,ab,kw OR 'blood stream infection*':ti,ab,kw) AND ('streptococcus'/exp OR 'enterococcus'/exp OR streptococcus:ti,ab,kw OR streptococcal:ti,ab,kw OR streptococci:ti,ab,kw OR enterococcus:ti,ab,kw OR enterococcal:ti,ab,kw OR enterococci:ti,ab,kw OR vre:ti,ab,kw OR 'vancomycin-resistant enterococc*':ti,ab,kw) AND ('follow-up blood culture*':ti,ab,kw OR 'repeat blood culture*':ti,ab,kw OR 'subsequent blood culture*':ti,ab,kw OR 'persistent bacteremia':ti,ab,kw OR 'persistent bacteraemia':ti,ab,kw OR 'bloodstream clearance':ti,ab,kw)
	Elsevier Scopus Advanced	TITLE-ABS-KEY(bacteremia OR bacteraemia OR "bloodstream infection*" OR "blood stream

Scopus	Search; inception through February 28, 2026	infection*") AND TITLE-ABS-KEY(Streptococcus OR streptococcal OR streptococci OR Enterococcus OR enterococcal OR enterococci OR VRE OR "vancomycin-resistant enterococc*") AND TITLE-ABS-KEY("follow-up blood culture*" OR "repeat blood culture*" OR "subsequent blood culture*" OR "persistent bacteremia" OR "persistent bacteraemia" OR "bloodstream clearance")
Web of Science Core Collection	Clarivate Web of Science Advanced Search; inception through February 28, 2026	TS=(bacteremia OR bacteraemia OR "bloodstream infection*" OR "blood stream infection*") AND TS=(Streptococcus OR streptococcal OR streptococci OR Enterococcus OR enterococcal OR enterococci OR VRE OR "vancomycin-resistant enterococc*") AND TS=("follow-up blood culture*" OR "repeat blood culture*" OR "subsequent blood culture*" OR "persistent bacteremia" OR "persistent bacteraemia" OR "bloodstream clearance")
Additional terms: PubMed	Supplementary focused search	Additional block: (endocarditis OR osteomyelitis OR "source control" OR "risk factor*" OR predictor* OR mortality OR relapse). Combine the complete PubMed search above with this block using AND.
Additional terms: Embase	Supplementary focused search	Additional block: (endocarditis OR osteomyelitis OR 'source control' OR 'risk factor*' OR predictor* OR mortality OR relapse):ti,ab,kw. Combine the complete Embase search above with this block using AND.
Additional terms: Scopus	Supplementary focused search	Additional block: TITLE-ABS-KEY(endocarditis OR osteomyelitis OR "source control" OR "risk factor*" OR predictor* OR mortality OR relapse). Combine the complete Scopus search above with this block using AND.
Additional terms: Web of Science	Supplementary focused search	Additional block: TS=(endocarditis OR osteomyelitis OR "source control" OR "risk factor*" OR predictor* OR mortality OR relapse). Combine the complete Web of Science search above with this block using AND.
Language restrictions	All databases	No language restrictions were applied.
Organism scope	All databases	Searches targeted streptococcal and enterococcal bloodstream infections, including vancomycin-resistant enterococci. Mixed-organism studies were eligible when relevant organism-specific findings were separately extractable.
Supplementary identification methods	Reference-list screening and forward-citation searching	Reference lists of included studies and relevant reviews were examined manually, and forward-citation searching was used to identify additional eligible studies.

TABLE 3: Database-specific search strategies, search coverage, and supplementary search terms.

MeSH, Medical Subject Headings; /exp, exploded Emtree heading; :ti,ab,kw, title, abstract, and author keywords; TITLE-ABS-KEY, title, abstract, and keywords; TS, Topic; VRE, vancomycin-resistant enterococci. The asterisk (*) indicates truncation.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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