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Consensus Statement | Infectious Diseases

Guidelines for Diagnosis and Management of Infective Endocarditis in Adults
A WikiGuidelines Group Consensus Statement

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Abstract

IMPORTANCE Practice guidelines often provide recommendations in which the strength of the recommendation is dissociated from the quality of the evidence.

OBJECTIVE To create a clinical guideline for the diagnosis and management of adult bacterial infective endocarditis (IE) that addresses the gap between the evidence and recommendation strength.

EVIDENCE REVIEW This consensus statement and systematic review applied an approach previously established by the WikiGuidelines Group to construct collaborative clinical guidelines. In April 2022 a call to new and existing members was released electronically (social media and email) for the next WikiGuidelines topic, and subsequently, topics and questions related to the diagnosis and management of adult bacterial IE were crowdsourced and prioritized by vote. For each topic, PubMed literature searches were conducted including all years and languages. Evidence was reported according to the WikiGuidelines charter: clear recommendations were established only when reproducible, prospective, controlled studies provided hypothesis-confirming evidence. In the absence of such data, clinical reviews were crafted discussing the risks and benefits of different approaches.

FINDINGS A total of 51 members from 10 countries reviewed 587 articles and submitted information relevant to 4 sections: establishing the diagnosis of IE (9 questions); multidisciplinary IE teams (1 question); prophylaxis (2 questions); and treatment (5 questions). Of 17 unique questions, a clear recommendation could only be provided for 1 question: 3 randomized clinical trials have established that oral transitional therapy is at least as effective as intravenous (IV)–only therapy for the treatment of IE. Clinical reviews were generated for the remaining questions.

CONCLUSIONS AND RELEVANCE In this consensus statement that applied the WikiGuideline method for clinical guideline development, oral transitional therapy was at least as effective as IV-only therapy for the treatment of IE. Several randomized clinical trials are underway to inform other areas of practice, and further research is needed.

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Key Points

Question Using the WikiGuidelines approach to the construct of clinical guidelines, how often can clear recommendations be made in the diagnosis and management of adult bacterial infective endocarditis?

Findings In this consensus statement, a panel of 51 members found that only 1 of 17 questions had sufficiently high-quality data to allow for a clear recommendation. Oral transitional therapy is at least as effective as intravenous-only therapy for the treatment of infective endocarditis.

Meaning These findings suggest that a higher quality of evidence needs to be established to guide the diagnosis and management of infective endocarditis.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Infective endocarditis (IE) is an ancient illness that can be difficult to diagnose and treat, leading to substantial morbidity and mortality even in the modern era. The literature regarding the management of IE spans decades but features few high-quality randomized clinical trials. This second WikiGuidelines consensus statement addresses the evidence-based management of IE. The guideline was drafted by an independent, international consortium of medical professionals who previously established a collaborative method to construct pragmatic, real-world, clinical practice guidelines.[1,2] WikiGuidelines provide clear recommendations when reproducible, high-quality data and/or hypothesis-confirming evidence is available and otherwise provide comprehensive clinical reviews summarizing different clinical approaches. WikiGuidelines offer clinician insights and are not intended to establish care mandates or medicolegal standards of care, nor to replace individual clinician judgment.

The intended end users are clinicians providing patient care across diverse settings (academic, community-based) and socioeconomic statuses (low-, middle-, or high-income countries), with varied experience (generalists or specialists). We incorporate the principles of high-value care (ie, right care, right place, right cost) and health care quality (ie, timely, safe, effective, efficient, equitable, patient-centered). As such, considerations of resource utilization, systems-based practice, reduction in health care waste, and harm reduction are intrinsic.

Feedback is solicited from many licensed practitioners to move away from guidelines constructed by subspecialty member organizations by invitation only. This allows for a more inclusive, broader representation of everyday care practitioners from across the world. We seek to change the traditional guidelines practice of creating care mandates based on expert opinion rather than hypothesis-confirming data, which risks societal-level harm by setting incorrect standards of care.[3-6] Following electronic polling of clinicians, we identified the next most preferred topic that could benefit from the WikiGuidelines approach: the diagnosis, prophylaxis, antibiotic therapy, and team-based management of bacterial IE in adults.

Methods

This guideline was crafted in accordance with the WikiGuidelines charter and follows the Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) reporting guideline.[7] The authorship team included 51 members from 10 countries (listed in eAppendix 1 in Supplement 1), including 31 MDs and 16 PharmDs with expertise in internal medicine, hospital medicine, infectious diseases and microbiology, cardiac surgery, cardiology, radiology, nephrology, and pharmacology. The charter specifies the process for selection of members (authors), conflict resolution, and for evidentiary and consensus standards used to review the literature. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system for evaluating the strength of evidence was replaced with a dichotomized approach of providing either clear recommendations or clinical reviews, due to published concerns with GRADE, including risk of bias, poor interrater reliability, and the dissociation between strength of recommendation and quality of evidence.[5,8,9]

High-quality, hypothesis-confirming data enable a clear recommendation and are based on at least 1 properly conducted, adequately powered randomized controlled trial (RCT) and at least 1 other concordant, prospective, controlled clinical study (either a second RCT, a quasi-experimental pre-post study, a pragmatic clinical trial, or a carefully conducted historically controlled study). In the absence of such data, to provide guidance that is permissive rather than proscriptive, WikiGuidelines provides clinical reviews that discuss clinical approaches, comparing risks and benefits. Recognizing the core ethical and clinical principle of first do no harm, consensus on routinely avoiding unsubstantiated care is permitted even in the absence of a clear recommendation.

On April 29, 2022, interested members were asked to submit their top questions on the diagnosis and management of endocarditis. Questions were thematically grouped into topic sections

and individual members volunteered to collaboratively author sections of interest. Sections had 1 or 2 team leaders and drafting team members who conducted literature reviews using PubMed or alternatives. There were no restrictions to searches, and all languages and dates were considered for inclusion. Following internal revision by topic group members, initial versions were revised by the first and senior authors and then circulated to all members participating in the guideline for further refinement. Drafting members could post questions electronically (social media or email) to receive open-source feedback on how to construct answers to questions that lacked hypothesis-confirming data. The second open round of revisions led to a final version of each topic, which then underwent a third round of revisions by all members. When feasible, for answers with more than 1 relevant study, meta-analysis was conducted using Stata version 17.0 (StataCorp).

Results

The tables and boxes included here are not intended to serve as recommendations in the traditional sense of guidelines. The information is often based on limited data, extrapolations, or both. Some of the content represents the authors' attempt to present reasonable clinical options based on their interpretations of imperfect published literature. A nuanced discussion of this information is contained in eAppendix 3 in Supplement 1.

Part 1: Establishing the Diagnosis of IE

Question 1: What Criteria Should Be Used to Establish the Diagnosis of IE? (Clinical Review)

The reference standard for diagnosis of IE is pathological confirmation. However, such information is virtually never available at the time when empirical therapeutic decisions must be made and, unless the patient undergoes surgical replacement of a valve, remains unavailable to confirm the diagnosis later. Several schemas have been developed over the years to guide clinicians in the diagnosis of IE absent pathological confirmation (eAppendix 2 in Supplement 1). Five of the 7 schema are based on the original Duke criteria and an iterative process that has aimed at improving sensitivity. Such schemas typically include clinical, microbiological, and imaging (eg, echocardiography or positron emission tomography [PET]) criteria. Schemas such as the modified Duke criteria (updated in 2023 to the Duke-ISCVID criteria[10]) are widely used and convenient for clinicians facilitating real-time diagnostic and therapeutic decision-making. However, there are no high-quality studies that definitively determine which diagnostic schema is most accurate, nor have head-to-head studies compared clinical outcomes between schemas. Studies that have reported the diagnostic accuracy have important limitations including retrospective designs, heterogeneous reference standards, and patient populations at variable risk of IE. It is therefore unclear how well schemas extrapolate to diverse care settings. Thus, no recommendation can be made regarding which, if any, are preferred for use. However, a structured approach to the diagnosis of IE is preferrable clinically and essential to guide research. Since most research studies apply the modified Duke criteria, these criteria likely accord with what most clinicians use.

Question 2: How Should Blood Culture Parameters Be Used to Inform Suspicion for IE? (Clinical Review)

Does Time-to-Positivity of Blood Cultures Predict IE? | Observational data suggest time-to-positivity (TTP) of blood cultures of less than 12 hours is associated with *Staphylococcus aureus* IE and independently predicts hospital mortality.[11] A similar study found that a shorter TTP was associated with IE in monomicrobial *Enterococcus faecalis* bacteremia (odds ratio [OR], 13.0; 95% CI, 4.4-38.0 in multivariate analysis).[12] TTP is likely influenced by the blood culture machine and/or bottles being used and by preexposure to antibiotics.[13]

How Long Should Blood Cultures Be Incubated in Suspected Cases of IE? | Observational data suggest that with modern culture techniques, a standard 5-day incubation for blood cultures is

adequate for almost all causes of IE.[14,15] Prolonged incubation could be considered in patients with prosthetic valve endocarditis (PVE) when *Cutibacterium acnes* is suspected.[14-16]

Does the Number of Blood Culture Sets Relate to the Diagnosis of IE? | Two large observational studies suggest that the maximum yield for recovering a pathogen from blood cultures is achieved with 3 (96%[17]-98%[18]) to 4 sets (99.8%[18]) over 24 hours, with each set comprising 2 × 10 mL filled bottles. Where possible, these should be taken prior to antibiotics, as the yield of blood cultures decreases after antibiotics are received.[19] The relationship between the number of positive blood culture sets and the diagnosis of IE requires additional study; however, growth in multiple vs single blood culture bottles is associated with IE in *S aureus* bacteremia and growth in 3 or more bottles is associated with IE in *E faecalis* bacteremia.[20,21]

Questions 3 and 4: How Can the Diagnoses of *Bartonella* and *Coxiella Burnetii* (Q Fever) IE Be Established? (Clinical Review)

There are limited published data to inform the accuracy of diagnostic testing for *Bartonella* IE, and published *C Burnetii* data have come from 1 center. While it may be reasonable to use an Ig G titer cutoff of at least 1:800 as diagnostic evidence of *Bartonella* IE, clinicians should be aware that the data set supporting accuracy of this cutoff is limited,[22] patients who do not have IE can have titers as high as 1:800 or higher, and patients can have lower titers but still have *Bartonella* as an etiology for IE.

The widely used serological cutoff to diagnose Q fever IE is a phase I IgG antibody titer of 1:800. However, validation of this titer cutoff was based on a 20-patient case series,[22] and no high-quality published studies have established its accuracy.

Question 5: What Is the Role of Molecular Rapid Diagnostic Testing in the Diagnosis of IE? (Clinical Review)

A systematic review and meta-analysis of molecular rapid diagnostic tests suggested improved outcomes in bloodstream infection when guided by antimicrobial stewardship programs[23]; however, no studies have assessed the impact on outcomes in IE. Where available, some clinicians use 16s rRNA testing of valve tissue in unsolved cases of culture-negative endocarditis, with a wide variability in sensitivity reported between studies.[24] Molecular diagnostic tests require further study before they can be routinely recommended, but they may be useful in select cases.

Question 6: What Is the Role of an Echocardiogram in the Diagnosis of IE? (Clinical Review)

In most cases of suspected IE, obtaining an echocardiogram represents usual care. Nonetheless, like any test, echocardiography should be ordered when it will inform management decisions.

Both the pretest probability of IE and study quality strongly affect the impact of transthoracic echocardiography (TTE) on patient treatment. A negative TTE may be adequate to rule out native valve endocarditis (NVE) if the initial pretest probability[25,26] is low (eg, <10%), or with a high-quality study, even if the pretest probability is moderate (eg, <25%).

Transesophageal echocardiography (TEE) is more sensitive than TTE for the diagnosis of IE. A TEE is most useful in specific scenarios: (1) to reduce the possibility of NVE where an unacceptably high posttest probability remains after a negative TTE (eg, 5%-10%) and where eliminating the diagnosis will change patient treatment; (2) in the evaluation of PVE where TTE has a lower sensitivity; and/or (3) to facilitate surgical planning or to evaluate for specific complications (eg, perivalvular abscess).

Not all centers have timely access to TEE (or TTE). Decisions regarding transfer to obtain an echocardiogram in resource-constrained settings need to be individualized.

Question 7: What Is the Role of Scoring Systems in the Identification of Patients Who May Require a TEE in the Diagnosis of IE? (Clinical Review)

Numerous clinical scoring systems have been developed to better identify patients who may benefit from invasive testing with TEE (eAppendix 2 in Supplement 1). Many have demonstrated high negative predictive values, which could be useful for resource stewardship. However, clinical prediction scores have important limitations. They have only been evaluated in retrospective studies, in some cases with relatively small numbers of patients with IE due to a single causative pathogen, with varied reference standards. Furthermore, there may be considerable selection bias and included patients may not be generalizable. Clinical prediction scores for IE have never been applied in a prospective study to demonstrate improved clinical outcomes or resource utilization. Scores may also be more complex than clinical criteria commonly used in clinical practice (eg, multiple positive blood cultures, time to clearance of bacteremia, and the presence of IE sequelae). Thus, the data are insufficient to make a clear recommendation.

Question 8: What Is the Role of Serial TTE for Assessing Progress of IE or Increasing the Diagnostic Sensitivity? (Clinical Review)

There are no high-quality data to support repeated or serial echocardiogram in patients with an initial negative study. Observational studies suggest repeated imaging may increase the diagnostic sensitivity but with unclear impact on patient outcomes.[27] If the result will change treatment (eg, alter antibiotic duration, prompt surgical evaluation), a repeated echocardiogram may be of value. Otherwise, routine use of follow-up or end-of-treatment TTE does not appear to provide a benefit to patients.

Question 9: What Is the Role of Fluorodeoxyglucose PET in the Diagnosis and Management of IE? (Clinical Review)

Numerous observational studies have evaluated the accuracy of 2-[18F]-fluorodeoxyglucose (18-FDG)–PET/computed tomography (CT) for the diagnosis of NVE, PVE, and cardiac device–related IE (CDIE). Meta-analyses have reported the sensitivity of 18F-FDG-PET/CT for NVE as poor, especially compared with PVE and CDIE; however, specificity remains high. Specifically, the pooled sensitivity and specificity of 18F-FDG-PET/CT for NVE was reported as 31% and 82% vs 73% and 80% for PVE and 87% and 94% CDIE.[28-30] Given its low sensitivity, a negative 18F-FDG-PET/CT cannot rule out a diagnosis of NVE, even in cases where there is a low pretest probability. It may be reasonable at appropriately resourced centers to use 18F-FDG-PET/CT for strongly suspected cases of PVE or CDIE in the presence of a negative or nondiagnostic TTE or TEE.

The ability of 18F-FDG-PET/CT to affect clinical outcomes has not been assessed for IE specifically, but observational studies have suggested 18F-FDG-PET/CT may increase detection of occult, secondary seeded sites of infection during *S aureus* bacteremia.[31] 18F-FDG-PET/CT is resource-intensive, not routinely available in all centers, and exposes patients to ionizing radiation, and whether use improves outcomes remains unknown.

Part 2: Multidisciplinary IE Teams

Question 1: Does a Multidisciplinary IE Team Improve Patient Outcomes? (Clinical Review)

Multidisciplinary IE teams may be comprised of experts in infectious diseases, pharmacy, cardiology, cardiac surgery, and depending on availability and the clinical presentation, specialists in radiology, neurology, stroke, general or vascular surgery, addiction medicine, and social services. Observational studies suggest the involvement of a multidisciplinary IE team may improve patient outcomes, including time to surgical intervention, and mortality.[32,33] However, there are no randomized clinical trials. There is also insufficient evidence to support routine transfer to a specialized referral center for treatment. If transfer is feasible, some clinicians may choose to do so to have more ready access to subspecialized services. Some higher risk complex populations that may benefit from a multidisciplinary team include persons who inject drugs (PWID), PVE, CDIE, presence of

hemodynamic instability, acute heart failure or cardiogenic shock, new severe valve regurgitation, perivalvular abscess, stroke, recurrent embolisms, or highly virulent and/or resistant organisms (eg, methicillin-resistant *S aureus* [MRSA][34]).

Part 3: Prophylaxis

Question 1: For Which Patients Is It Appropriate to Prescribe Antibiotic Prophylaxis to Prevent IE? (Clinical Review)

Antibiotic prophylaxis of endocarditis risks toxic effects and selects for antibiotic resistance, causing societal-level harm.[35] Consequently, WikiGuidelines authors prefer limiting prophylaxis to patients who both are perceived to be at higher risk for IE (prosthetic cardiac valves or retained prosthetic material used for cardiac valve repair; cardiac transplant recipients with valve regurgitation; congenital cyanotic heart diseases unrepaired or with residual shunt; and those with a history of IE[36]) and who are undergoing dental procedures where there is likely a greater risk of bacteremia (eg, manipulation of the gingival tissue or periapical region around the teeth, or perforation of the oral mucosa).[36] Of note, a 2022 study by Vähäsarja et al[37] found no increased incidence of oral streptococcal IE among high-risk individuals following a recommendation to no longer administer antibiotic prophylaxis in dentistry. More evidence is required to support any recommendation regarding prophylaxis for gastrointestinal, genitourinary, respiratory, or skin and soft tissue procedures.[38] If used, the risks of antimicrobial prophylaxis may be partly mitigated by using a single dose rather than longer courses.

Question 2: Which Antibiotics Are Appropriate for Antibiotic Prophylaxis to Prevent IE? (Clinical Review)

No high-quality data inform relative efficacy of various prophylaxis regimens to prevent IE. Nevertheless, given the known microbiology of procedurally related cases of IE, it is rational to select prophylactic antibiotics that are active against viridans group *Streptococci* (VGS). Oral administration is preferred, with penicillins and cephalosporins associated with a lower rate of *Clostridioides difficile* infection when compared with clindamycin.[39] There are no RCTs in support of one agent vs another; however, amoxicillin seems to be the most commonly used and carries the lowest risk of adverse events overall (**Table 1**).[36,40,41]

Part 4: Treatment

Question 1: What Empirical Therapy Should Be Considered for IE? (Clinical Review)

Little high-quality evidence is available to guide selection of empirical therapy for known or suspected IE. Observational studies have suggested that IE outcomes may be improved by consulting infectious diseases experts.[42,43] Empirical regimens are generally selected to cover the most likely potential causes based on the history and physical examination incorporating risk factors or clues for the source of infection and/or local antimicrobial resistance patterns (which may differ

Table 1. Potential Single-Dose Antibiotics for Infective Endocarditis Prophylaxis Based on Antimicrobial Coverage and Risk Mitigation in the Absence of High-Quality, Comparative Studies[a]

Route and allergies	Antibiotic	Dose
Oral	Amoxicillin	2 g
Parenteral (unable to take oral antibiotics)	Ampicillin	2g IM or IV
	Cefazolin	1g IM or IV
	Ceftriaxone	1g IM or IV
Oral (allergic to penicillin)	Cephalexin	2 g
	Azithromycin	500 mg
	Clarithromycin[b]	500 mg
	Doxycycline	100 mg
Parenteral (unable to take oral antibiotics and allergic to penicillin or ampicillin)	Cefazolin[c]	1 g IM or IV

Abbreviations: IM, intramuscular; IV, intravenous.

[a] Note that there are many possible agents and the evidence in favor of one over another is limited. This table is provided as a reference for those which are most used.

[b] Clarithromycin has an increased risk of drug-drug interactions.

[c] Cefazolin has very little risk of cross-reactivity to penicillin or ampicillin.[40]

by geographic location). In general, a combination of vancomycin or daptomycin (to cover MRSA, *Enterococcus spp*, and in the case of prosthetic valve, coagulase-negative staphylococci[44]) and a β-lactam like ceftriaxone (if suspecting an odontogenic or gastrointestinal focus) or cefazolin (if suspecting methicillin-susceptible *S aureus* [MSSA]) may be reasonable, although alternative regimens are also possible and there is almost no direct comparative evidence (**Box 1**; eAppendix 3 in Supplement 1).[48-50] Absent comparative outcomes studies, some authors prefer a daptomycin dose of 8 to 10 mg/kg if *S aureus* is suspected[51] and 10 to 12 mg/kg if enterococcus is being targeted.[52] To minimize harm, the aminoglycosides and rifampin are best reserved for definitive therapy, if used at all.

Question 2: What Are Potential Definitive Intravenous-Based Treatment Options for IE? (Clinical Review)

Definitive antibiotic therapy recommended for IE depends on the etiologic organism, its susceptibility, patient factors (eg, comorbidity, allergy), and whether the infection is of a native or prosthetic valve. This treatment regimen complexity has limited the availability of high-quality comparative outcomes studies. In general, the addition of adjunctive agents (eg, β-lactam,

Box 1. Rational Choices of Empirical Antimicrobial Therapy Based on Likely Microbiology

This box lists reasonable options based largely on historical practice and in vitro susceptibility, with little clinical data to validate relative efficacies for most regimens. It is best practice to select regimens based on specific clinical situations and patient/local epidemiology. Please see the eAppendix 3 in Supplement 1.

Native Valve

Principal Agent

- Vancomycin: the principal agent most authors use is vancomycin, as it has the most evidence and will cover *Streptococcus aureus*, streptococci, and most enterococci. Note that none of the principal agents may be required in native valve endocarditis if there is minimal clinical concern for MRSA or coagulase-negative staphylococci or enterococci since monotherapy with cefazolin or ceftriaxone may suffice.
- Daptomycin: daptomycin may offer some advantages in terms of pharmacokinetics and the local net financial and clinical resources required with a similar spectrum of activity. Most authors prefer a dose of 8 to 10 mg/kg if *S aureus* is being targeted or 10 to 12 mg/kg if enterococcus is being targeted.
- Alternative, linezolid: linezolid can be an alternative for patients where there are challenges in obtaining or maintaining intravenous access, where there is reasonable concern for vancomycin-resistant organisms, or where both vancomycin and daptomycin are precluded (eg, vancomycin allergy and pneumonia).

Second Agent

- Ceftriaxone: ceftriaxone is preferred by some WikiGuidelines authors as a second agent since it has superior coverage for streptococcal species and HACEK organisms. Yet, there are times when *S aureus* is more likely clinically.
- Cefazolin: The combination of vancomycin or daptomycin and cefazolin is synergistic for MRSA in vivo without evidence of increased nephrotoxicity.[45] For MSSA, there is observational evidence that beta-lactam therapy is superior to vancomycin therapy, and for this reason many authors prefer to include a beta-lactam with good *S. aureus* activity. Most WikiGuidelines authors prefer cefazolin over anti-staphylococcal penicillins in this context due to decreased toxicity, with similar clinical efficacy described in recent observational studies.[46,47]

Prosthetic Valve

Principal Agent

- Vancomycin
- Daptomycin: Most authors prefer a dose of 8 to 10 mg/kg if *S aureus* is being targeted or 10 to 12 mg/kg if enterococcus is being targeted.
- Alternative, linezolid

Second Agent

- Early (<3 mo)
  - For early prosthetic valve infection, choice of the second agent is driven primarily by the local microbiology of gram-negative bacterial infections. It may be desirable to avoid carbapenem therapy due to the need to preserve them for more resistant cases, although in some regions, empirical use may be necessary depending on local microbiology. For early prosthetic valve disease, ceftriaxone could have inferior nosocomial gram-negative coverage, depending on local microbiology.
  - Cefepime
  - Piperacillin-tazobactam
  - Carbapenem
  - Ceftriaxone
- Later (>3 months):
  - Ceftriaxone
  - Amoxicillin-clavulanate (IV)
  - Ampicillin-sulbactam
  - Cefazolin

Abbreviations: IV, intravenous; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-susceptible *S aureus*.

aminoglycosides, rifampin) requires a careful consideration of the risks and benefits and an acknowledgment of the limitations of the evidence.[53] Most WikiGuidelines authors suggest against routine use of adjunctive aminoglycosides because of a lack of evidence of benefit with a demonstrable risk of harm (discussed in eAppendix 3 in Supplement 1). Options for definitive intravenous therapy by organism are presented in **Table 2**, with nuanced discussions in eAppendix 3 in Supplement 1.[54-60]

Question 3: Can Oral Antimicrobial Therapy Be Used to Treat IE? (Clear Recommendation)

We can provide a clear recommendation for this question. Three randomized clinical trials have established that transition from initial intravenous therapy to oral therapy is at least as effective as intravenous-only therapy for the treatment of IE.[55,61,62] These results are also supported by pharmacologic data demonstrating that many oral antibiotics achieve adequate levels in blood to exceed the minimum inhibitory concentrations (MICs) of target pathogens, as well as numerous observational studies of oral therapy for IE demonstrating favorable outcomes.[63] Importantly, intravenous-only therapy has never been established to be superior to modern oral antimicrobial therapy in any clinical trial or observational study of patients with IE. Therefore, after factoring in considerations presented in eAppendix 3 in Supplement 1, transition to oral therapy from initial intravenous therapy is a reasonable option for treating patients with IE.

Table 2. Options for Definitive IV Therapy Regimens Presuming Organism Is Susceptible[a]

Organisms	Preferred primary treatment	Adjunctive agent/setting	Alternatives
Streptococci (penicillin MIC <0.5 µmol/L)	• Ceftriaxone 2 g daily • Penicillin G 4 million U every 4 h[b] • Ampicillin/amoxicillin 2 g every 4 h[b]	For penicillin nonsusceptible strains (MICs 0.25-0.5 µmol/L), gentamicin 3 mg/kg/d	• Vancomycin dosed by level[c,d] • Linezolid 600 mg twice daily[e]
Streptococci (penicillin MIC >0.5-2 µmol/L)	• Ceftriaxone 2 g daily • Vancomycin dosed by level[c,d,f]	For penicillin nonsusceptible strains (MICs 0.5-2.0 µmol/L), gentamicin 3 mg/kg/d[d]	Linezolid 600mg twice daily[e]
Methicillin-susceptible staphylococci	• Cefazolin 2 g every 8 h[g] • (Flu)cloxacillin, oxacillin, nafcillin 2 g IV every 4 h	For prosthetic valve endocarditis, rifampin 600 mg daily or twice daily or 300 mg three time daily[h]	• Vancomycin dosed by level[c] • Daptomycin 6-10 mg/kg/d[i] • Linezolid 600mg twice daily[e,j]
Methicillin-resistant staphylococci	• Vancomycin dosed by level[c] • Daptomycin 6-10 mg/kg/d[i]	For prosthetic valve endocarditis, rifampin 600 mg daily or twice daily or 300 mg three times daily[h]	Linezolid 600 mg twice daily[e,j]
Enterococci non-VRE[k]	• Ampicillin or amoxicillin 2 g every 4 h • Vancomycin dosed by level[c,d]	• With ampicillin or amoxicillin, ceftriaxone 2 g every 12 h or gentamicin 3 mg/kg/d[k] • For vancomycin, gentamicin 3 mg/kg/d[k]	NA
HACEK	Ceftriaxone 2 g daily	NA	• Levofloxacin 750 mg daily • Ciprofloxacin 400 mg twice daily
Other gram-negative bacteria	Parenteral β-lactam with in vitro activity against microorganism and good pharmacokinetics for bloodstream infection	NA	• Levofloxacin 750 mg daily • Ciprofloxacin 400 mg twice daily • Moxifloxacin 400 mg daily

Abbreviations: IV, intravenous; HACEK, *Haemophilus, Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*; MIC, minimum inhibitory concentration; NA, not applicable.

[a] This table lists reasonable options based largely on historical practice and in vitro susceptibility, with little clinical data to validate relative efficacies for most regimens. It may be reasonable to use alternative regimens based on specific clinical situations.

[b] Penicillin G and ampicillin require more human resources (frequent dosing) and can cost more than ceftriaxone.

[c] Vancomycin dosed per local standard, by area under the receiver operating curve, or by trough (10-15 µg/mL) targets.

[d] Combination vancomycin and gentamicin are associated with more toxic effects and may be best avoided.

[e] Linezolid data are limited. Some suggest that early monotherapy might be avoided for high bacterial inoculums.

[f] For penicillin-resistant viridans group streptococci, some authors preferred vancomycin monotherapy to ceftriaxone and gentamicin.

[g] No high-quality data have confirmed the cefazolin inoculum effect is clinically important when treating IE. Recent observational data suggest cefazolin is effective to treat methicillin-susceptible staphylococci bacteremia/IE with a lower adverse event rate than oxacillin/nafcillin.[54]

[h] Data are unclear regarding benefit of adjunctive rifampin or gentamicin.[53] Gentamicin has more risk of harm and most authors do not recommend use. Rifampin, if used, was dosed at 600mg twice daily in POET.[55]

[i] For daptomycin, the published randomized clinical trial for *S aureus* bacteremia used 6 mg/kg/d[56]; however, many clinicians feel that higher doses (of 8-10 mg/kg) are warranted to prevent treatment failure.[51] The monograph indication is for right-sided endocarditis.

[j] Data for linezolid for methicillin-susceptible *S aureus* and methicillin-resistant *S aureus* are limited.

[k] For *Enterococcus faecium*, the combination of ampicillin and gentamicin is not supported by high-quality data. If used, 2 weeks of gentamicin may provide most of the benefit while mitigating toxic effects.[57-59] The combination of ampicillin and ceftriaxone is associated with similar cure rates and fewer adverse events.[60] It is not known whether ampicillin is as effective. For discussion of *E faecium*, refer to eAppendix 2 in Supplement 1.

Question 4: If Oral Antimicrobial Therapy Is Used in the Treatment of IE, Are There Preferred Agents, Is a Specific Duration of Intravenous Lead-In Therapy Necessary, and What Are Reasonable Clinical Criteria for Patient Selection? (Clinical Review)

Not all oral antimicrobial agents are likely candidates for treatment of IE. Historical experience suggests that older sulfonamides, tetracyclines, and macrolides may lead to poor outcomes perhaps related to low achievable blood levels relative to target MICs.[64-66] Trimethoprim-sulfamethoxazole was inferior as a lead-in option for the treatment of staphylococcal IE in 2 RCTs.[45,67] If oral therapy is used, it is rational to select antibiotics demonstrated to have efficacy in published studies (**Table 3** and **Box 2**).[46,47,55,61,62,68-71,73-77] It is unclear whether dual regimens, such as those used in the POET study,[55] are required, as other data have demonstrated favorable outcomes with certain monotherapy regimens (Table 2; eAppendix 3 in Supplement 1). It is also unclear to what extent intravenous lead-in therapy is needed prior to transitioning to oral therapy, as studies have used a wide range of intravenous lead-in prior to oral therapy, including 1 RCT with no intravenous lead-in.[62] Reasonable patient selection criteria for oral therapy may include (1) clinical stability with no immediate indication for procedural source control or cardiac surgery; and (2) bacteremia has cleared or is clearing without the need for source control; and (3) an oral antibiotic regimen is available to which the etiologic organism is susceptible in vitro and which is supported by published clinical data; and (4) the patient is likely to absorb the antibiotic from the gastrointestinal tract; and (5) there are no socioeconomic determinants of health or inequities rendering intravenous therapy the preferred route.

Question 5: What Is the Recommended Duration of Antimicrobial Therapy for IE? (Clinical Review)

Left-Sided IE | Evidence to support durations of treatment for IE are almost entirely observational, and most durations are based on historical practice. One RCT[78] established that penicillin-susceptible streptococcal endocarditis treated with 2 weeks of combination therapy with ceftriaxone and gentamicin resulted in similar outcomes as 4 weeks of ceftriaxone monotherapy.[78] Whether combination therapy is necessary is addressed in eAppendix 3 in Supplement 1.

For other pathogens, and in absence of data, the historical practice has been to treat staphylococcal and enterococcal left-sided endocarditis for 6 weeks and *Haemophilus, Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella* (HACEK) endocarditis for 4 weeks.

Table 3. Summary of Oral Transitional Antibiotics Used in Published Clinical Studies[a]

Drug	Organism	Dose	References
Amoxicillin	• Sensitive streptococci (with or without combination treatment) • Enterococci (only in combination with rifampin or linezolid)	1 g 4 times daily	Iversen et al,[55] 2019; Stamboulian et al,[61] 1991
Dicloxacillin	Sensitive staphylococci (data from RCT only in combination with rifampin)	1 g 4 times daily	Iversen et al, 2019[55]
Levofloxacin[b]	Sensitive staphylococci (only in combination with rifampin)	750 mg once daily	Iversen et al,[55] 2019; Heldman et al,[62] 1996
Moxifloxacin	Sensitive streptococci, enterococci, or staphylococci (only in combination with amoxicillin, rifampin, or linezolid)	400 mg once daily	Iversen et al,[55] 2019
TMP-SMX	Sensitive staphylococci	960 mg or 4800 mg daily in divided doses	Tissot-Dupont et al,[46] 2019; Freling et al,[47] 2023
Linezolid	Sensitive gram-positive cocci (alone or in combination with rifampin, moxifloxacin, or amoxicillin)[c]	600 mg twice daily	Iversen et al,[55] 2019; Tascini et al,[68] 2011; Falagas et al,[69] 2006; Colli et al,[70] 2007; Muñoz et al,[71] 2007; Freling S et al,[47] 2023
Rifampin	Only as adjunctive agent (as previously described)	600 mg once or twice daily	Iversen et al,[55] 2019; Heldman et al,[62] 1996; Acocella G,[72] 1983; Freling et al,[47] 2023

Abbreviations: RCT, randomized clinical trial; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Combination regimens were used in the largest RCT; other published regimens have included either monotherapy or combination therapy regimens.[3]

[b] The study used ciprofloxacin rather than levofloxacin, the latter of which was not yet clinically available. However, in ensuing years, ciprofloxacin experienced rapid emergence of staphylococcal resistance. Levofloxacin or moxifloxacin are preferred to ciprofloxacin due to enhanced in vitro activity against staphylococci, but generally only in combination with a second agent.

[c] For most patients in published studies, linezolid was used alone; but in some references,[3,4,12] linezolid was given in combination with rifampin, moxifloxacin, or amoxicillin.

Recommendations to treat PVE for 6 weeks are also based on opinion rather than high-quality data. Ongoing RCTs SATIE[79] and POET II[80] should help to establish optimal durations.

Right-Sided IE | For uncomplicated right-sided IE caused by MSSA (defined as lacking intracardiac or systemic complications of infection), prospective observational studies and 1 RCT conducted in the PWID population[81] suggest that 2 weeks of combination antibiotic therapy might result in similar cure rates as longer courses. However, both 2-week treatment groups in the only RCT[81] had a lower-than-expected combined treatment success in the intention-to-treat population (mean, 72% [95% CI, 63%-81%]), and the observational studies all had major limitations. Optimal durations of therapy for uncomplicated right-sided IE outside of the PWID population and/or caused by other pathogens are unknown. In the absence of evidence, WikiGuidelines authors feel it may be reasonable in carefully selected cases (eAppendix 3 in Supplement 1) to use a similar duration of therapy for other pathogens as for MSSA. For patients with complicated right-sided IE, no data are available to guide duration of therapy, and longer courses are often used without any supporting evidence.

Discussion

IE is associated with high morbidity and mortality. Despite extensive literature discussing the management of IE, we found that most aspects of diagnosis and management are based on historical practice and small, outdated, observational studies. High-quality studies can inform only 1 clear recommendation: oral transitional antibiotics for the treatment of IE. This paucity of high-quality evidence will change with the arrival of results of several much-needed ongoing RCTs.

Box 2. Summary of Oral Step-Down Antibiotics by Organism[a]

Streptococci: penicillin-sensitive (MIC ≤0.12 μg/ml)
- Amoxicillin 1 g 4 times daily, only for native valve infection[b]
- Amoxicillin 1 g 4 times daily with rifampin 600 mg once daily
- Linezolid 600 mg twice daily alone or with rifampin 600 mg once daily
- Moxifloxacin 400 mg once daily with rifampin 600 mg once daily or linezolid 600 mg twice daily

Streptococci: penicillin-intermediate (MIC 0.25-1.00 μg/mL) or *Enterococcus*
- Amoxicillin 1 g 4 times daily with rifampin 600 mg once daily or linezolid 600 mg twice daily
- Linezolid 600 mg twice daily alone or with rifampin 600 mg once daily
- Moxifloxacin 400 mg once daily with rifampin 600 mg once daily

Streptococci: penicillin-resistant (MIC ≥2 μg/mL) or amoxicillin-resistant *Enterococcus*
- Linezolid 600 mg twice daily alone or with (rifampin 600 mg once daily)
- Moxifloxacin 400 mg once daily with rifampin 600 mg once daily

***Staphylococcus* spp**
- Levofloxacin 750 mg once daily with rifampin 600 mg once daily or linezolid 600 mg twice daily
- Linezolid 600 mg twice daily alone or in combination with rifampin 600 mg once daily (rifampin lowers linezolid blood levels, so whether monotherapy or combination therapy is preferred remains unclear)
- TMP-SMX 960 mg or 4800 mg daily in divided doses[c]
- Dicloxacillin 1 g 4 times daily plus rifampin 600 mg once daily (only for methicillin-sensitive strains)

Abbreviations: MIC, minimum inhibitory concentration; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Combination regimens were used in the largest randomized clinical trial; other published regimens have included either monotherapy or combination therapy regimens.[3]

[b] Amoxicillin monotherapy was studied in a 30-patient randomized clinical trial with excellent outcomes,[1] whereas dual therapy was used in a substantially larger randomized clinical trial.[3] Thus, it is not clear that rifampin is needed for sensitive streptococci, but there are more data for the combination.

[c] If used for transitioning from intravenous to oral therapy, the dosing of TMP-SMX is uncertain. The quasi-experimental study used a very high dose equivalent to 3 double-strength tablets twice daily, which had a relatively high rate of intolerance.[46] Many WikiGuidelines authors prefer to use lower doses, such as 2 double-strength tablets twice daily; 1 double-strength tablet twice daily may be conceivably sufficient, but there are currently no published data demonstrating efficacy of such a dose.

Limitations

This study has limitations, primarily the lack of high-quality studies. The entire area of treatment in terms of antibiotic prophylaxis, empirical therapy, selection of optimal antibiotic classes, and almost all permutations of durations of therapy are based on case series or small observational studies. Again, very few (or no) head-to-head trials of different therapeutic options exist. It was striking to observe how much of the management of IE is currently based on historical practice or expert opinion. Although oral antibiotics to complete treatment of IE have the strongest evidence, this approach still lags in clinical practice. Much of the observational evidence also has very important limitations with respect to the diagnosis of IE as the criterion standard varies between studies, there is obvious selection and immortal time bias present, and few studies use pathologically confirmed IE.

Conclusions

This consensus statement highlights the lack of high-quality evidence that supports most of the modern practices in diagnosis and management of bacterial IE in adults. This study represents data available as of June 1, 2023. Clinicians who believe other evidence should be considered are encouraged to contact the authors to propose revisions to the online living version of this guideline. As previously stated, no clinical trial or knowledge synthesis can extrapolate to all possible patient care scenarios; hence, this guideline is not intended to establish medicolegal standards of care or replace clinician judgment for individual patients.

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REFERENCES

1. Spellberg B, Aggrey G, Brennan MB, et al; WikiGuidelines Group. Use of novel strategies to develop guidelines for management of pyogenic osteomyelitis in adults: a WikiGuidelines Group consensus statement. *JAMA Netw Open*. 2022;5(5):e2211321. doi:10.1001/jamanetworkopen.2022.11321

2. Wikiguidelines. Accessed July 3, 2023. https://www.wikiguidelines.com/

3. Spellberg B, Wright WF, Shaneyfelt T, Centor RM. The future of medical guidelines: standardizing clinical care with the humility of uncertainty. *Ann Intern Med*. 2021;174(12):1740-1742. doi:10.7326/M21-3034

4. Spellberg B, Shorr AF. Opinion-based recommendations: beware the tyranny of experts. *Open Forum Infect Dis*. 2021;8(11):ofab490. doi:10.1093/ofid/ofab490

5. Wright WF, Jorgensen SCJ, Spellberg B. Heaping the pelion of vancomycin on the ossa of methicillin-resistant *Staphylococcus aureus*: back to basics in clinical care and guidelines. *Clin Infect Dis*. 2021;72(10):e682-e684. doi:10.1093/cid/ciaa1360

6. Packer M. The room where it happens: a skeptic's analysis of the new heart failure guidelines. *J Card Fail*. 2016;22(9):726-730. doi:10.1016/j.cardfail.2016.07.433

7. Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf*. 2016;25(12):986-992. doi:10.1136/bmjqs-2015-004411

8. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD

9. Shaneyfelt TM, Centor RM. Reassessment of clinical practice guidelines: go gently into that good night. *JAMA*. 2009;301(8):868-869. doi:10.1001/jama.2009.225

10. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-ISCVID Criteria for Infective Endocarditis: updating the Modified Duke Criteria. *Clin Infect Dis*. 2023;ciad271. doi:10.1093/cid/ciad271

11. Kahn F, Resman F, Bergmark S, et al. Time to blood culture positivity in Staphylococcus aureus bacteraemia to determine risk of infective endocarditis. *Clin Microbiol Infect*. 2021;27(9):1345.e7-1345.e12. doi:10.1016/j.cmi.2020.11.007

12. Oldberg K, Thorén R, Nilson B, Gilje P, Inghammar M, Rasmussen M. Short time to blood culture positivity in Enterococcus faecalis infective endocarditis. *Eur J Clin Microbiol Infect Dis*. 2021;40(8):1657-1664. doi:10.1007/s10096-021-04210-9

13. Butler-Laporte G, Yansouni CP, Paquette K, et al. Real-world time to positivity of 2 widely used commercial blood culture systems in patients with severe manifestations of sepsis: an analysis of the FABLED Study. *Open Forum Infect Dis*. 2020;7(9):ofaa371. doi:10.1093/ofid/ofaa371

14. Fihman V, Faury H, Moussafeur A, et al. Blood cultures for the diagnosis of infective endocarditis: what is the benefit of prolonged incubation? *J Clin Med*. 2021;10(24):5824. doi:10.3390/jcm10245824

15. Lourtet-Hascoët J, Pilmis B, Mizrahi A, Van JCN, Le Monnier A. Does prolonged blood culture incubation improve microbiological diagnosis of HACEK and slow-growing bacteria infective endocarditis? *Eur J Clin Microbiol Infect Dis*. 2019;38(5):989-990. doi:10.1007/s10096-019-03550-x

16. Fida M, Dylla BL, Sohail MR, Pritt BS, Schuetz AN, Patel R. Role of prolonged blood culture incubation in infective endocarditis diagnosis. *Eur J Clin Microbiol Infect Dis*. 2019;38(1):197-198. doi:10.1007/s10096-018-3397-1

17. Cockerill FR III, Wilson JW, Vetter EA, et al. Optimal testing parameters for blood cultures. *Clin Infect Dis*. 2004;38(12):1724-1730. doi:10.1086/421087

18. Lee A, Mirrett S, Reller LB, Weinstein MP. Detection of bloodstream infections in adults: how many blood cultures are needed? *J Clin Microbiol*. 2007;45(11):3546-3548. doi:10.1128/JCM.01555-07

19. Cheng MP, Stenstrom R, Paquette K, et al; FABLED Investigators. Blood Culture results before and after antimicrobial administration in patients with severe manifestations of sepsis: a diagnostic study. *Ann Intern Med*. 2019;171(8):547-554. doi:10.7326/M19-1696

20. Go JR, Challener D, Corsini Campioli C, et al. Clinical significance of *Staphylococcus aureus* in a single positive blood culture bottle. *Open Forum Infect Dis*. 2021;9(2):ofab642. doi:10.1093/ofid/ofab642

21. Dahl A, Iversen K, Tonder N, et al. Prevalence of infective endocarditis in *Enterococcus faecalis* bacteremia. *J Am Coll Cardiol*. 2019;74(2):193-201. doi:10.1016/j.jacc.2019.04.059

22. Fournier PE, Casalta JP, Habib G, Messana T, Raoult D. Modification of the diagnostic criteria proposed by the Duke Endocarditis Service to permit improved diagnosis of Q fever endocarditis. *Am J Med*. 1996;100(6):629-633. doi:10.1016/S0002-9343(96)00040-X

23. Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. *Clin Infect Dis*. 2017;64(1):15-23. doi:10.1093/cid/ciw649

24. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. *J Clin Microbiol*. 2017;55(9):2599-2608. doi:10.1128/JCM.00635-17

25. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Arch Intern Med*. 2003;163(17):2066-2072. doi:10.1001/archinte.163.17.2066

26. Østergaard L, Voldstedlund M, Bruun NE, et al. Prevalence and mortality of infective endocarditis in community-acquired and healthcare-associated *Staphylococcus aureus* bacteremia: a Danish nationwide registry-based cohort study. *Open Forum Infect Dis*. 2022;9(12):ofac647. doi:10.1093/ofid/ofac647

27. Vieira MLC, Grinberg M, Pomerantzeff PMA, Andrade JL, Mansur AJ. Repeated echocardiographic examinations of patients with suspected infective endocarditis. *Heart*. 2004;90(9):1020-1024. doi:10.1136/hrt.2003.025585

28. Albano D, Dondi F, Gazzilli M, Giubbini R, Bertagna F. Meta-analysis of the diagnostic performance of ^{18}F-FDG-PET/CT imaging in native valve endocarditis. *JACC Cardiovasc Imaging*. 2021;14(5):1063-1065. doi:10.1016/j.jcmg.2020.09.021

29. Juneau D, Golfam M, Hazra S, et al. Positron emission tomography and single-photon emission computed tomography imaging in the diagnosis of cardiac implantable electronic device infection: a systematic review and meta-analysis. *Circ Cardiovasc Imaging*. 2017;10(4):e005772. doi:10.1161/CIRCIMAGING.116.005772

30. Wang TKM, Sánchez-Nadales A, Igbinomwanhia E, Cremer P, Griffin B, Xu B. Diagnosis of infective endocarditis by subtype using ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography: a contemporary meta-analysis. *Circ Cardiovasc Imaging*. 2020;13(6):e010600. doi:10.1161/CIRCIMAGING.120.010600

31. Thottacherry E, Cortés-Penfield NW. Evidence of clinical impact supports a new petition for Medicare coverage of 2-[18F]fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography in the evaluation of *Staphylococcus aureus* bacteremia: a focused literature review and call to action. *Clin Infect Dis*. 2022;75(8):1457-1461. doi:10.1093/cid/ciac363

32. Kaura A, Byrne J, Fife A, et al. Inception of the 'endocarditis team' is associated with improved survival in patients with infective endocarditis who are managed medically: findings from a before-and-after study. *Open Heart*. 2017;4(2):e000699. doi:10.1136/openhrt-2017-000699

33. Chirillo F, Scotton P, Rocco F, et al. Impact of a multidisciplinary management strategy on the outcome of patients with native valve infective endocarditis. *Am J Cardiol*. 2013;112(8):1171-1176. doi:10.1016/j.amjcard.2013.05.060

34. Davierwala PM, Marin-Cuartas M, Misfeld M, Borger MA. The value of an "endocarditis team". *Ann Cardiothorac Surg*. 2019;8(6):621-629. doi:10.21037/acs.2019.09.03

35. Beacher N, Sweeney MP, Bagg J. Dentists, antibiotics and *Clostridium difficile*-associated disease. *Br Dent J*. 2015;219(6):275-279. doi:10.1038/sj.bdj.2015.720

36. Wilson WR, Gewitz M, Lockhart PB, et al; American Heart Association Young Hearts Rheumatic Fever, Endocarditis and Kawasaki Disease Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Cardiovascular and Stroke Nursing; and the Council on Quality of Care and Outcomes Research. Prevention of viridans group streptococcal infective endocarditis: a scientific statement from the American Heart Association. *Circulation*. 2021;143(20):e963-e978. doi:10.1161/CIR.0000000000000969

37. Vähäsarja N, Lund B, Ternhag A, et al. Infective endocarditis among high-risk individuals before and after the cessation of antibiotic prophylaxis in dentistry: a national cohort study. *Clin Infect Dis*. 2022;75(7):1171-1178. doi:10.1093/cid/ciac095

38. Thornhill MH, Crum A, Campbell R, et al. Temporal association between invasive procedures and infective endocarditis. *Heart*. 2023;109(3):223-231. doi:10.1136/heartjnl-2022-321519

39. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. *Antimicrob Agents Chemother*. 2013;57(5):2326-2332. doi:10.1128/AAC.02176-12

40. Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the frequency of dual allergy to penicillins and cefazolin: a systematic review and meta-analysis. *JAMA Surg*. 2021;156(4):e210021. doi:10.1001/jamasurg.2021.0021

41. Thornhill MH, Dayer MJ, Durkin MJ, Lockhart PB, Baddour LM. Risk of adverse reactions to oral antibiotics prescribed by dentists. *J Dent Res*. 2019;98(10):1081-1087. doi:10.1177/0022034519863645

42. Bai AD, Showler A, Burry L, et al. Impact of infectious disease consultation on quality of care, mortality, and length of stay in *Staphylococcus aureus* bacteremia: results from a large multicenter cohort study. *Clin Infect Dis*. 2015;60(10):1451-1461. doi:10.1093/cid/civ120

43. Yamamoto S, Hosokawa N, Sogi M, et al. Impact of infectious diseases service consultation on diagnosis of infective endocarditis. *Scand J Infect Dis*. 2012;44(4):270-275. doi:10.3109/00365548.2011.638317

44. Murdoch DR, Corey GR, Hoen B, et al; International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169(5):463-473. doi:10.1001/archinternmed.2008.603

45. Paul M, Bishara J, Yahav D, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant *Staphylococcus aureus*: randomised controlled trial. *BMJ*. 2015;350:h2219. doi:10.1136/bmj.h2219

46. Tissot-Dupont H, Gouriet F, Oliver L, et al. High-dose trimethoprim-sulfamethoxazole and clindamycin for *Staphylococcus aureus* endocarditis. *Int J Antimicrob Agents*. 2019;54(2):143-148. doi:10.1016/j.ijantimicag.2019.06.006

47. Freling S, Wald-Dickler N, Banerjee J, et al. Real-world application of oral therapy for infective endocarditis: a multicenter retrospective, cohort study. *Clin Infect Dis*. Published online March 7, 2023. doi:10.1093/cid/ciad119

48. Tong SYC, Lye DC, Yahav D, et al; Australasian Society for Infectious Diseases Clinical Research Network. Effect of vancomycin or daptomycin with vs without an antistaphylococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: a randomized clinical trial. *JAMA*. 2020;323(6):527-537. doi:10.1001/jama.2020.0103

49. Lefèvre B, Hoen B, Goehringer F, et al; for AEPEI study group (Association pour l'Etude et la Prévention de l'Endocardite Infectieuse). Antistaphylococcal penicillins vs cefazolin in the treatment of methicillin-susceptible Staphylococcus aureus infective endocarditis: a quasi-experimental monocentre study. *Eur J Clin Microbiol Infect Dis*. 2021;40(12):2605-2616. doi:10.1007/s10096-021-04313-3

50. Lecomte R, Bourreau A, Deschanvres C, et al. Comparative outcomes of cefazolin versus antistaphylococcal penicillins in methicillin-susceptible *Staphylococcus aureus* infective endocarditis: a post hoc analysis of a prospective multicentre French cohort study. *Clin Microbiol Infect*. 2021;27(7):1015-1021. doi:10.1016/j.cmi.2020.08.044

51. Jones TW, Jun AH, Michal JL, Olney WJ. High-dose daptomycin and clinical applications. *Ann Pharmacother*. 2021;55(11):1363-1378. doi:10.1177/1060028021991943

52. Adema JL, Lake LN, Stevens RW, et al. Understanding and application of daptomycin-susceptible dose-dependent category for *Enterococcus*: a mixed-methods study. *Open Forum Infect Dis*. 2022;9(1):ofab611. doi:10.1093/ofid/ofab611

53. Ryder JH, Tong SYC, Gallagher JC, et al. Deconstructing the dogma: systematic literature review and meta-analysis of adjunctive gentamicin and rifampin in staphylococcal prosthetic valve endocarditis. *Open Forum Infect Dis*. 2022;9(11):ofac583. doi:10.1093/ofid/ofac583

54. Weis S, Kesselmeier M, Davis JS, et al. Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with *Staphylococcus aureus* bacteraemia. *Clin Microbiol Infect*. 2019;25(7):818-827. doi:10.1016/j.cmi.2019.03.010

55. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med*. 2019;380(5):415-424. doi:10.1056/NEJMoa1808312

56. Fowler VG Jr, Boucher HW, Corey GR, et al; S. aureus Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355(7):653-665. doi:10.1056/NEJMoa053783

57. Dahl A, Rasmussen RV, Bundgaard H, et al. *Enterococcus faecalis* infective endocarditis: a pilot study of the relationship between duration of gentamicin treatment and outcome. *Circulation*. 2013;127(17):1810-1817. doi:10.1161/CIRCULATIONAHA.112.001170

58. Buchholtz K, Larsen CT, Hassager C, Bruun NE. Severity of gentamicin's nephrotoxic effect on patients with infective endocarditis: a prospective observational cohort study of 373 patients. *Clin Infect Dis*. 2009;48(1):65-71. doi:10.1086/594122

59. Olaison L, Schadewitz K; Swedish Society of Infectious Diseases Quality Assurance Study Group for Endocarditis. Enterococcal endocarditis in Sweden, 1995-1999: can shorter therapy with aminoglycosides be used? *Clin Infect Dis*. 2002;34(2):159-166. doi:10.1086/338233

60. Mirna M, Topf A, Schmutzler L, Hoppe UC, Lichtenauer M. Time to abandon ampicillin plus gentamicin in favour of ampicillin plus ceftriaxone in *Enterococcus faecalis* infective endocarditis? a meta-analysis of comparative trials. *Clin Res Cardiol*. 2022;111(10):1077-1086. doi:10.1007/s00392-021-01971-3

61. Stamboulian D, Bonvehi P, Arevalo C, et al. Antibiotic management of outpatients with endocarditis due to penicillin-susceptible streptococci. *Rev Infect Dis*. 1991;13(suppl 2):S160-S163. doi:10.1093/clinids/13.Supplement_2.S160

62. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. *Am J Med*. 1996;101(1):68-76. doi:10.1016/S0002-9343(96)00070-8

63. Wald-Dickler N, Holtom PD, Phillips MC, et al. Oral is the new IV—challenging decades of blood and bone infection dogma: a systematic review. *Am J Med*. 2022;135(3):369-379.e1. doi:10.1016/j.amjmed.2021.10.007

64. Finland M. Treatment of bacterial endocarditis. *N Engl J Med*. 1954;250(9):372-383. doi:10.1056/NEJM195403042500906

65. Finland M. Treatment of bacterial endocarditis. *N Engl J Med*. 1954;250(10):419-428. doi:10.1056/NEJM195403112501005

66. Roantree RJ, Rantz LA. Fatal staphylococcal endocarditis treated with erythromycin; rapid development of resistance in vivo and in vitro. *AMA Arch Intern Med*. 1955;95(2):320-325. doi:10.1001/archinte.1955.00250080142011

67. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med*. 1992;117(5):390-398. doi:10.7326/0003-4819-117-5-390

68. Tascini C, Bongiorni MG, Doria R, et al. Linezolid for endocarditis: a case series of 14 patients. *J Antimicrob Chemother*. 2011;66(3):679-682. doi:10.1093/jac/dkq506

69. Falagas ME, Manta KG, Ntziora F, Vardakas KZ. Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. *J Antimicrob Chemother*. 2006;58(2):273-280. doi:10.1093/jac/dkl219

70. Colli A, Campodonico R, Gherli T. Early switch from vancomycin to oral linezolid for treatment of gram-positive heart valve endocarditis. *Ann Thorac Surg*. 2007;84(1):87-91. doi:10.1016/j.athoracsur.2007.02.096

71. Muñoz P, Rodríguez-Creixéms M, Moreno M, Marín M, Ramallo V, Bouza E; Game Study Group. Linezolid therapy for infective endocarditis. *Clin Microbiol Infect*. 2007;13(2):211-215. doi:10.1111/j.1469-0691.2006.01585.x

72. Acocella G. Pharmacokinetics and metabolism of rifampin in humans. *Rev Infect Dis*. 1983;5(suppl 3):S428-S432. doi:10.1093/clinids/5.Supplement_3.S428

73. Martí-Carvajal AJ, Dayer M, Conterno LO, Gonzalez Garay AG, Martí-Amarista CE. A comparison of different antibiotic regimens for the treatment of infective endocarditis. *Cochrane Database Syst Rev*. 2020;5(5):CD009880. doi:10.1002/14651858.CD009880.pub3

74. Spellberg B, Chambers HF, Musher DM, Walsh TL, Bayer AS. Evaluation of a paradigm shift from intravenous antibiotics to oral step-down therapy for the treatment of infective endocarditis: a narrative review. *JAMA Intern Med*. 2020;180(5):769-777. doi:10.1001/jamainternmed.2020.0555

75. Davar K, Clark D, Centor RM, et al. Can the future of ID escape the inertial dogma of its past? the exemplars of shorter is better and oral is the new IV. *Open Forum Infect Dis*. 2022;10(1):ofac706. doi:10.1093/ofid/ofac706

76. Rezar R, Lichtenauer M, Haar M, et al. Infective endocarditis—a review of current therapy and future challenges. *Hellenic J Cardiol*. 2021;62(3):190-200. doi:10.1016/j.hjc.2020.10.007

77. Brown E, Gould FK. Oral antibiotics for infective endocarditis: a clinical review. *J Antimicrob Chemother*. 2020;75(8):2021-2027. doi:10.1093/jac/dkaa106

78. Sexton DJ, Tenenbaum MJ, Wilson WR, et al; Endocarditis Treatment Consortium Group. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. *Clin Infect Dis*. 1998;27(6):1470-1474. doi:10.1086/515038

79. Olmos C, Vilacosta I, López J, et al. Short-course antibiotic regimen compared to conventional antibiotic treatment for gram-positive cocci infective endocarditis: randomized clinical trial (SATIE). *BMC Infect Dis*. 2020;20(1):417. doi:10.1186/s12879-020-05132-1

80. Østergaard L, Pries-Heje MM, Hasselbalch RB, et al. Accelerated treatment of endocarditis—the POET II trial: rationale and design of a randomized controlled trial. *Am Heart J*. 2020;227:40-46. doi:10.1016/j.ahj.2020.05.012

81. Ribera E, Gómez-Jimenez J, Cortes E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided Staphylococcus aureus endocarditis: a randomized, controlled trial. *Ann Intern Med*. 1996;125(12):969-974. doi:10.7326/0003-4819-125-12-199612150-00005

SUPPLEMENT 1.

eAppendix 1. Study Participants
eAppendix 2. Executive Summary
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eReferences.

SUPPLEMENT 2.

Data Sharing Statement