Open Forum Infectious Diseases

MAJOR ARTICLE

Infective Endocarditis Guidelines: The Challenges of Adherence—A Survey of Infectious Diseases Clinicians

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Background. Guidelines exist to aid clinicians in managing patients with infective endocarditis (IE), but the degree of adherence with guidelines by Infectious Disease (ID) physicians is largely unknown.

Methods. An electronic survey assessing adherence with selected IE guidelines was emailed to 1409 adult ID physician members of the Infectious Diseases Society of America's Emerging Infections Network.

Results. Five hundred fifty-seven physicians who managed IE responded. Twenty percent indicated that ID was not consulted on every case of IE at their hospitals, and 13% did not recommend transthoracic echocardiography (TTE) for all IE cases. The duration of antimicrobial therapy was timed from the first day of negative blood cultures by 91% of respondents. Thirty-four percent of clinicians did not utilize an aminoglycoside for staphylococcal prosthetic valve IE (PVE). Double β-lactam therapy was "usually" or "almost always" employed by 83% of respondents for enterococcal IE. For patients with active IE who underwent valve replacement and manifested positive surgical cultures, 6 weeks of postoperative antibiotics was recommended by 86% of clinicians.

Conclusions. The finding that adherence was <90% with core guideline recommendations that all patients with suspected IE be seen by ID and that all patients undergo TTE is noteworthy. Aminoglycoside therapy of IE appears to be declining, with double β-lactam regimens emerging as the preferred treatment for enterococcal IE. The duration of postoperative antimicrobial therapy for patients undergoing valve replacement during acute IE is poorly defined and represents an area for which additional evidence is needed.

Keywords. infective endocarditis; guidelines; management; adherence; clinical practice.

Guidelines for managing infective endocarditis (IE) were first introduced by the American Heart Association (AHA) in 1989 [1], with the most recent update in 2015 [2]. The European Society of Cardiology (ESC) has developed similar guidelines [3]. The goal of both documents is to facilitate application of knowledge and best practices for diagnosing and managing IE.

Rates of IE have recently increased in the United States and globally [4, 5]. As IE has become resurgent, old challenges in providing care have resurfaced and new management dilemmas have emerged [6, 7]. Guidelines exist to address clinical uncertainties and to inform practice. However, based on our observations, there appears to be substantial practice variation in the application of guidelines to the diagnosis and management of adult patients with IE. Several potential obstacles to guideline adherence exist: (1) Multiple guidelines are available, some of which offer differing recommendations, thus leading to confusion rather than clarity in their application. (2) Guidelines have evolved from succinct, "bullet-point" documents to voluminous works that are often challenging to read. (3) Healthy skepticism exists about the level of evidence in many guidelines, as consensus expert opinion, case series, and/or standard of care form the basis for some recommendations [8]. In the 2015 AHA document, 81 (58.7%) of 138 recommendations were Level C in quality [2]. (4) Practitioners realize that guidelines do not always reflect realities of clinical practice and that compromises in care must be made, sometimes in response to patient preferences [9].

Accepting the conclusion that guidelines are important adjuncts in management, our goal was to better understand current clinical practices in the care of patients with IE. Accordingly, we developed a survey to assess adherence to selected guidelines for managing IE in adults, as outlined in recent AHA and ESC documents [2, 3].

METHODS

An electronic survey consisting of 17 multiple-choice questions and 2 case scenarios (Supplementary Figure 1) was sent to physician members of the Infectious Diseases Society of America's Emerging Infections Network (EIN) [10] with adult

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ID practices in the United States, Puerto Rico, and Canada. The EIN is funded by the Centers for Disease Control and Prevention to serve as a provider-based surveillance network for emerging infections and related phenomena. Approximately 20% of ID physicians in clinical practice in the United States volunteer as EIN members. The survey was distributed by email or facsimile on February 12, 2020, with 2 reminders at weekly intervals for nonrespondents. An opt-out option was provided for those who indicated that they did not manage IE. Respondents were not required to answer all questions, so total responses for individual questions varied. As used in the survey, the term "some" implied <50%, "usually" equated to 50–90%, and "almost always" referred to >90% of the time. EIN staff tabulated responses and analyzed data. Categorical variables were compared using a χ^2 test or Fisher exact test with SAS, version 9.4 (Cary, NC). *P* values <.05 were considered significant.

RESULTS

Participant Characteristics

Of 1409 active EIN physician members, 631 (45%) responded to the survey. Respondents were significantly more likely than nonrespondents to have ≥25 years of ID experience ($P < .0001$) and to be employed by a Veterans Affairs hospital ($P = .009$). No other significant differences were identified. Of the 631 respondents, 74 (12%) indicated that they did not manage IE, so they opted out.

General Approaches to the Diagnosis and Management of IE

Eighty percent of respondents indicated that ID was consulted for every suspected case of IE, whereas Cardiothoracic Surgery was consulted in only a minority of cases (17%) (Figure 1). A designated endocarditis team existed in only 6% of hospitals. Transthoracic echocardiography (TTE) was recommended by most clinicians (87%) for all cases of IE, while only 32% of respondents ordered transesophageal echocardiography (TEE) for all IE cases. In patients with positive blood cultures, most respondents (95%, 530/557) repeated cultures until negative. The duration of antimicrobial therapy was generally timed from the first day on which blood cultures were negative (91% of respondents; 508/557).

End-of-Therapy Management

End-of-therapy (EOT) echocardiography was recommended by 44% of respondents, with 89% recommending TTE and 11% TEE (Figure 1). EOT blood cultures were ordered by 181 (32%) physicians, with the timing of those blood cultures ranging from 48 hours to 6 weeks. Recognized risk factors for relapse

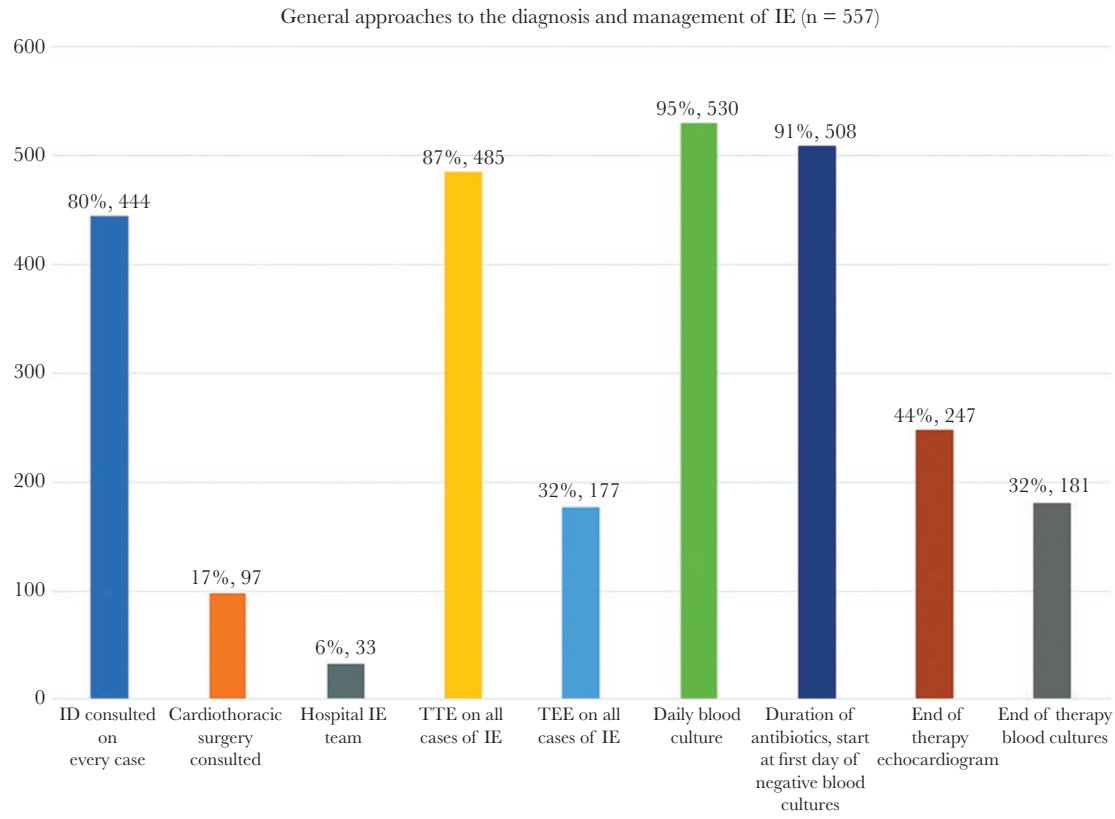

Figure 1. General approaches to the diagnosis and management of infective endocarditis. Abbreviations: ID, Infectious Diseases; IE, infective endocarditis; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

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such as endovascular hardware, specific pathogens (ie, *S. aureus*), or delayed response to therapy were the identified indications for EOT cultures.

Treatment of Specific Pathogens Causing IE

For treatment of native valve IE (NVE) due to methicillin-susceptible *S. aureus* (MSSA), only 4% of respondents preferred combination antimicrobial therapy (Table 1). When queried as to whether cefazolin monotherapy was adequate for MSSA IE, 89% of respondents replied affirmatively. Only 66% of physicians indicated that they used an aminoglycoside as a component of combination therapy for staphylococcal prosthetic valve endocarditis (PVE). The specifics of aminoglycoside usage in this setting are shown in Table 1. For enterococcal IE, 83% of respondents (n = 461/557) stated that they "usually" (27%) or "almost always" (56%) employed ampicillin and ceftriaxone (A + C) as their regimen of choice (Figure 2). Conversely, only 16% selected traditional treatment with penicillin (or ampicillin or vancomycin) plus an aminoglycoside as their preferred ("usually" or "almost always") therapy. If an aminoglycoside was used, 60% treated for 2 weeks only, whereas 39% selected 4–6 weeks. For those practitioners utilizing A + C for enterococcal IE, 44% restricted usage to *E. faecalis* only, while 47% used A + C for any enterococcal species. Seventy-six percent of respondents employed A + C for both NVE and PVE, whereas 17% limited usage to NVE only.

Table 1. Treatment of Specific Pathogens Causing Infective Endocarditis

Pathogen/Type Infective Endocarditis	Yes, No. (%)	No, No. (%)	No Answer, No. (%)
Methicillin-susceptible *Staphylococcus aureus* native valve IE			
Is combination antimicrobial therapy used for treatment?	23 (4)	527 (95)	7 (1)
Is cefazolin monotherapy adequate?	487 (89)	54 (10)	6 (1)
Enterococcal IE			
Preferred treatment (usually + almost always)			
β-lactam or vancomycin + aminoglycoside	90 (16)	411 (74)	56 (10)
Ampicillin + ceftriaxone	461 (83)	92 (17)	4 (1)
Do you ever use an aminoglycoside?	416 (75)	141 (25)	—
If used, what is the aminoglycoside duration?			
2 wk	251 (60)		
4–6 wk	161 (39)		
If an aminoglycoside is used, do you obtain a baseline audiogram?	177 (42)	222 (54)	17 (4)
If you treat with A + C, is it used for:			
Only *Enterococcus faecalis*	240 (44)		
Any *Enterococcus* species	259 (47)		
Native valve IE only	92 (17)		
Prosthetic valve IE only	5 (1)		
Both native and prosthetic valve IE	417 (76)		
Staphylococcal prosthetic valve IE			
Do you use an aminoglycoside for treatment?	369 (66)	188 (34)	
What aminoglycoside dosage is used?			
3 mg/kg/d	311 (84)		
5–8 mg/kg/d	39 (11)		
How do you dose the aminoglycoside?			
Once daily	168 (46)		
In divided doses	183 (50)		
How many patients complete 2 weeks?			
Some (<50%)	76 (21)		
Usually (50%–90%)	204 (55)		
Almost always (>90%)	70 (19)		
What dose of rifampin is used?			
300 mg 2×/d	308 (55)		
300 mg 3×/d	166 (30)		
Other	31 (6)		
Do not use	39 (7)		

Abbreviations: A + C, ampicillin + ceftriaxone; IE, infective endocarditis.

Case Scenarios

In scenario #1, a patient with mitral NVE due to methicillin-resistant *S. aureus* (MRSA) underwent valve replacement. At the time of surgery, 2 full weeks of therapy had been completed, 1 week of which was after bacteremia cleared. Surgical gram stain

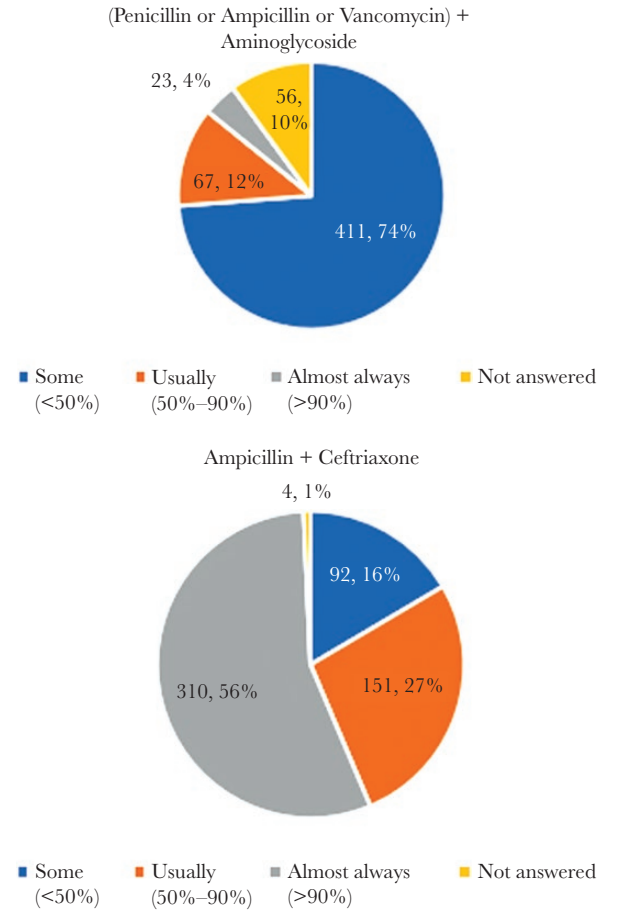

Figure 2. Treatment strategies in enterococcal endocarditis.

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and culture were negative. Survey participants were asked how long they would continue antibiotics postoperatively. Responses were diverse, with 9% choosing 2 weeks, 30% selecting 4 weeks, 39% electing 5 weeks, and 20% treating for 6 weeks.

The clinical features of scenario #2 were identical to #1, except that surgical cultures grew MRSA. In that scenario, 86% of respondents chose to treat for 6 weeks after surgery. As an additional query, it was asked if respondents would treat the patient postoperatively for NVE or PVE as the prosthesis potentially was placed in an "infected" field. Fifty-five percent elected to manage the patient for PVE, 33% opted for an NVE regimen, and 11% were unsure.

DISCUSSION

Despite decades of clinical experience and availability of guidelines since 1989 [1], management dilemmas continue to challenge clinicians caring for patients with IE [6, 7]. Guidelines are designed to assist clinicians with meeting those challenges and, accordingly, are updated regularly [2, 3]. However, AHA IE guidelines are qualified by the statement that "recommendations be used to support and not supplant decisions in individual patient management" [2]. That statement tacitly acknowledges that information used to formulate guidelines may change rapidly and that guidelines may reflect expert opinion rather than evidence derived from clinical trials [8]. Given those limitations, the degree of adherence with IE guidelines in real-world clinical practice may vary. Tissont-Dupont and colleagues examined adherence with antibiotic therapy recommendations for IE and found that overall global compliance was only 58% [11]. If guidelines are to improve patient outcomes, and data supporting that conclusion do exist for other infections [12], then higher levels of adherence with IE guidelines are desirable. This survey was developed to provide a "snapshot" of adherence with selected IE guidelines by a representative sample of practicing ID clinicians in North America.

As this survey reflects, general approaches to diagnosing and managing IE vary and may not conform strictly with published guidelines [2, 3]. AHA guidelines recommend ID consultation for every suspected case of IE [2]. However, 20% of practitioners indicated that all cases of IE were not seen by ID at their hospitals. That "selective" approach is perhaps consistent with ESC guidelines, which suggest that patients with "noncomplicated" IE can be managed initially at nonreference centers [3]. Even though no study has specifically evaluated the impact of ID consultation on IE outcomes, numerous studies have demonstrated benefits of ID consultation for complex infections [13], and IE is certainly 1 such infection. Only 17% of respondents reported that cardiothoracic surgery was routinely consulted for every case of IE. Both AHA and ESC guidelines emphasize a multidisciplinary "team" approach, typically involving cardiothoracic surgery [2, 3]. Whether that implies that preemptive cardiothoracic surgery consultation should be obtained for all patients is not addressed. Several publications have examined the benefits of an "endocarditis team," with a general consensus that those teams favorably impact IE-related mortality [14]. Despite the enthusiasm for endocarditis teams in Europe, only 6% of US and Canadian respondents indicated that their primary hospital had such a team. In terms of routine diagnostic testing, 87% of respondents recommended TTE for all patients with IE, which is in keeping with both US and European guidelines [2, 3]. For patients with positive blood cultures, 95% of respondents repeated blood cultures on a daily or every-other-day basis until negative, though that recommendation is not specifically delineated in the guidelines [2, 3]. Ninety-one percent of clinicians dated the duration of therapy as beginning on the first day on which blood cultures were negative, an approach consistent with both US and European recommendations [2, 3].

EOT management of IE is largely nonstandardized. Both the AHA and ESC recommend an EOT echocardiogram [2, 3] though the recommendation from the ESC is "stronger." In our survey cohort, 44% of respondents recommended EOT echocardiography, 89% of whom suggested TTE. A recent study by Virk et al. reported that 73% of their IE patients underwent EOT echocardiography [15]. Those authors suggested that EOT echocardiography could perhaps be targeted toward patients with new or worsening symptoms/signs at the EOT evaluation. Whereas the AHA does not recommend routine EOT blood cultures [2], the ESC indicates that EOT blood cultures should be obtained at the initial post-therapy visit [3]. Among ID clinicians taking our survey, 32% ordered EOT blood cultures, but there was no well-defined point at which EOT blood cultures were obtained. No studies examining the utility of EOT blood cultures were identified.

Several survey questions addressed the preferred antimicrobial therapy for specific organisms. For NVE due to MSSA, monotherapy was viewed as adequate, which conforms with recommendations [2, 3]. Eighty-nine percent of respondents expressed confidence with cefazolin as monotherapy for MSSA NVE, which is listed as an alternative for penicillin-allergic patients in US guidelines [2] but is not mentioned as an option in European guidelines [3]. Of note, a recent study raised questions about using cefazolin in high-inoculum infections such as IE [16]. Even though both AHA and ESC guidelines recommend initial triple therapy, which includes rifampin and an aminoglycoside, for staphylococcal PVE [2, 3], 34% of respondents did not use an aminoglycoside in that setting. Based on those results, it might be concluded that aminoglycoside therapy for staphylococcal PVE is perhaps "falling out of favor." A recent retrospective study from Spain [17] and a narrative review from France [18] both suggested that aminoglycoside use in staphylococcal PVE may not be necessary. In contrast to the tepid embrace of aminoglycosides for staphylococcal PVE, 91% of those surveyed reported using rifampin. Both

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Ramos-Martinez et al. [17] and Lebeaux and colleagues [18] endorsed rifampin as the critical component of combination therapy for staphylococcal PVE.

As reflected by this survey, therapy for enterococcal IE has undergone a notable evolution over the past decade. Aminoglycoside-containing regimens have long been the cornerstone for treating enterococcal IE [2], and both US and European guidelines still have a β-lactam plus gentamicin as the "first" regimen listed in their tables outlining therapy for enterococcal strains susceptible to both penicillin and gentamicin [2, 3]. However, double β-lactam regimens are included as an acceptable alternative based on accumulating evidence that supports the efficacy and safety of that regimen for enterococcal IE [19, 20]. It should be noted, however, that data from prospective clinical trials comparing β-lactam + aminoglycoside therapy with A + C for the treatment of enterococcal IE are not currently available. In this survey of US and Canadian physicians, the combination of A + C was preferred by the majority of respondents for treating enterococcal IE. In contrast, only 16% of ID clinicians "usually" or "almost always" treated enterococcal IE with penicillin plus an aminoglycoside. Forty-seven percent of respondents felt comfortable using A + C for any enterococcal species (not just *E. faecalis*), and 76% utilized A + C for both NVE and PVE. Use of A + C for all enterococcal species is counter to ESC recommendations, which suggest that A + C should NOT be used for *E. faecium* IE given the high likelihood of ampicillin resistance [3].

The case scenarios attempted to address management dilemmas that arise in patients who undergo valve replacement during active IE. In the first, the patient underwent mitral valve replacement after completing 2 weeks of preoperative antibiotic therapy with 1 week of negative blood cultures before surgery and negative surgical cultures. Five weeks was the most commonly selected duration for postoperative antimicrobial therapy and is consistent with AHA and ESC recommendations [2, 3] but responses were quite varied. The diversity of opinions likely reflects the limited evidence available to inform decision-making. Studies by Morris and colleagues [21], Munoz et al. [22], and Rao et al. [23] all concluded that 2–3 weeks of therapy after surgery was probably sufficient for most patients if surgical cultures were negative. However, the AHA opted for a more conservative approach, stating that it was reasonable to count the days of therapy given preoperatively in the overall duration of treatment for culture-negative patients [2]. Similarly, the ESC indicated that the duration of treatment was based upon the first day of effective antibiotic therapy, which was usually the date of the first negative blood culture [3].

In the second scenario, surgical cultures were positive at valve replacement surgery. Most respondents (86%) administered 6 additional weeks of therapy postoperatively, an approach consistent with both AHA and ESC guidelines [2, 3]. As an additional decision point in the second case, respondents were asked whether postoperative treatment should be that utilized for NVE or for PVE. Fifty-five percent chose to treat for PVE, whereas 33% elected to treat as NVE. Although not offering a formal recommendation for that scenario, the AHA states that there is a lack of consensus as to whether the postsurgical regimen should be the one for PVE or NVE in patients who undergo implantation of prosthetic valves during treatment for active IE [2]. In contrast, the ESC indicates that the postoperative regimen should be that recommended for NVE, not for PVE [3]. A retrospective review from the Mayo Clinic examining that issue concluded that cure rates were similar whether an NVE or PVE regimen was utilized postoperatively [24].

This survey had strengths as well as limitations. Strengths of the survey included the geographic diversity of the respondents and the good response rate. Factors perhaps contributing to the above-average response rate were the use of a defined population of ID clinicians assembled from a professional organization who "agreed" to participate in surveys through membership in the EIN and the topic itself, which apparently resonated with the respondents because of its timeliness [4, 5] and the associated challenges in management [6, 7]. Limitations were several. First, it was restricted to ID clinicians in the United States and Canada and did not include colleagues in other parts of the world whose use of guidelines may differ from practices in North America. Second, the survey was based upon self-reported data from a subset of voluntary respondents who may not be representative of the larger group of ID clinicians in the United States and Canada as a whole, thus leading to possible selection bias. Response bias is a third concern, as survey answers may not accurately reflect practice patterns in all geographic areas. Fourth, it is conceivable that respondents answered questions based upon their knowledge of the guidelines rather than their actual clinical practice, which was not the intent of the survey. Fifth, the survey focused primarily upon intravenous antimicrobial therapy for IE and did not explore the rapidly evolving use of oral regimens for IE [25]. Last, the timing of the survey coincided with onset of the COVID-19 pandemic, which may have limited participation.

Needless to say, there are numerous other questions pertaining to the management of IE that were not addressed by the current survey [6]. For example, what criteria could be used to determine which patients might benefit from early cardiovascular surgery consultation? Should neuroimaging be performed before valve replacement surgery in all patients or only in selected patients, and if the latter, which patients? Is there a role for anticoagulation in managing patients with IE? Do alternative cardiac imaging modalities such as high-resolution cardiac computed tomography or positron emission tomography scanning offer any diagnostic advantages beyond echocardiography? Which patients are appropriate for outpatient parenteral antibiotic therapy or oral step-down therapy? Additionally, a number of responses in the current survey might benefit from

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further clarification. For example, what are the impediments to establishing endocarditis teams? Why is TEE utilized less frequently than might be expected? Why is A + C used to treat non-*faecalis* enterococcal IE? A future follow-up survey could possibly be a useful tool for further defining the basis for clinical practices that are not guideline-adherent.

In conclusion, this survey offered interesting insights about management of IE by ID clinicians in the United States and Canada. Importantly, guideline adherence appeared to be suboptimal, as 20% of respondents reported that ID did not evaluate all suspected cases of IE and 13% did not recommend TTE for all IE patients. Those 2 guidelines are perhaps "essential," so adherence at levels below 90% is concerning. Second, even though a "team" approach to IE management is generally embraced as an important principle, only 6% of respondents indicated that their hospitals had a designated endocarditis team. Third, it appears that aminoglycoside use in IE is declining and that double β-lactam therapy is the preferred treatment for enterococcal IE. Last, duration of postoperative therapy for patients undergoing valve replacement during acute IE remains unclear and represents an area for additional investigation.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Questions or comments should be addressed to the corresponding author.

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