Patient Selection Criteria and Management Guidelines for Outpatient Parenteral Antibiotic Therapy for Native Valve Infective Endocarditis

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Outpatient parenteral antibiotic therapy (OPAT) for infective endocarditis (IE) is being applied widely, despite the absence of controlled data that demonstrates that outcomes are equivalent to those with standard inpatient antibiotic therapy. We review existing OPAT guidelines, published data on the timing of complications from IE, and data on risk factors that can be used to predict complications. These data are used to propose more stringent criteria for patient selection and clinical management of OPAT for native valve IE. We recommend a conservative approach (inpatient or daily outpatient follow-up) during the critical phase (weeks 0–2 of treatment), when complications are most likely, and we recommend consideration of OPAT for the continuation phase (weeks 2–4 or 2–6 of treatment) when life-threatening complications are less likely.

Principles of therapy for infective endocarditis (IE) have emerged from 50 years of clinical experience [1–3]. The practice of using 4–6 weeks of bactericidal parenteral therapy grew out of unsuccessful treatment attempts with less aggressive therapy. Historically, patients remained hospitalized during the majority of their treatment course, received inpatient parenteral antibiotic therapy, were often on bed rest, and were assessed daily for signs of ongoing cardiac infection, heart failure, heart block or arrhythmia, metastatic complications of IE, and adverse effects of antibiotics. Approximately 25% of patients underwent valve replacement surgery while they were hospitalized with IE [4], frequently on an urgent basis.

Recently, this model of inpatient care has been in flux in the wake of successes with shorter courses of therapy, the ability to administer outpatient parenteral antibiotic therapy (OPAT) [5], and economic pressures that dictate shorter hospital stays [6, 7]. Many patients with IE now receive OPAT for some portion of their treatment [8, 9], even though the data on effects of OPAT on IE outcomes in large cohorts is limited. Recent experience with 2 patients who had ultimately fatal outcomes after they received OPAT for IE prompted us to review existing guidelines. These guidelines for OPAT for IE emphasize the essential quality components of such care and specify that inpatients must be medically stable before the institution of OPAT. However, they do not provide a rationale for, or explicit recommendations for, determining the timing of the transition from inpatient parenteral antibiotic therapy to OPAT [10, 11]. Our review suggested that existing data on risk factors for adverse outcomes in patients with IE and on the timing of IE complications provided a basis for more stringent guidelines on both patient selection for and timing of OPAT for IE.

CLINICAL EXPERIENCE WITH OPAT

OPAT has gained popularity in the past 5 years, and data on its use for selected cases of IE continue to accumulate [12–19]. The literature on OPAT for IE reports excellent patient outcomes, but these studies have used careful patient selection and management. It is not clear that results are comparable with wider and more routine use of OPAT in clinical practice. Patients with uncomplicated viridans streptococcal IE and some *Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae* (HACEK)

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group infections have been considered candidates for OPAT, whereas patients with complications such as congestive heart failure or major emboli are usually excluded [20–24].

The major prospective studies of shorter regimens for patients with viridans streptococcal IE have used a median of 8 days of initial inpatient therapy (table 1) [25–28]. Patients with acute staphylococcal or enterococcal endocarditis and culture-negative IE have been deemed less suitable candidates for OPAT [29]. Of importance, the data on OPAT for *Staphylococcus aureus* IE that have been published have involved only 26 patients [30]. Rehm [30] has concluded that more data are required about the safety and efficacy of OPAT for *S. aureus* IE. In a 1993 review [31], it was recommended that controlled trials be conducted to compare the outcomes of OPAT with those of inpatient parenteral antibiotic therapy before assuming that the 2 therapies have equal efficacy; such trials have not been published.

Our experience involved 2 patients who had fatal outcomes after they received OPAT for IE. We were consulted regarding these patients when they were admitted to our institution with life-threatening complications after OPAT. A patient with *S. aureus* IE was discharged in stable condition after receiving 1 week of inpatient therapy. While at home on OPAT, fever recurred. Surgery was performed for an annular abscess, and the patient died 1 week later after a complicated postoperative course. A second patient had viridans streptococcal IE and was discharged in stable condition after 1 week of inpatient antibiotic therapy. While at home on OPAT, the patient developed dyspnea. Physician reevaluation was done and diagnosis of congestive heart failure was made 48 hours later. The patient died that day, shortly after he was admitted with severe aortic insufficiency related to perivalvular abscess. Although it is not clear that earlier diagnoses would have prevented fatal outcomes for these patients, both complications were potentially curable with earlier operative intervention, and, therefore, we considered it possible that OPAT contributed to the adverse outcomes.

MORTALITY ASSOCIATED WITH IE

Current estimated mortality rates have a range of 4%–9% for patients with viridans streptococcal disease and 25%–47% for patients with *S. aureus* infection [32–35]. Acute infection of <2 weeks' duration, especially with *S. aureus,* has a particularly poor prognosis and is associated with valve ring abscess in up to 30% of cases [4, 36–39]. Aortic valve *S. aureus* IE correlates with higher rates of heart failure, central nervous system complications, and mortality [40–42]. Other virulent pathogens, including *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Neisseria meningitidis,* and *Neisseria gonorrhoeae* may also cause acute IE syndromes [37]. Additional organisms that can cause high mortality rates include enterococci (15%–20% [32, 33, 43]), certain hemolytic streptococci (groups B, C, and G; 13%–20% [44]), and *Enterobacteriaceae, Pseudomonas,* and fungi (>50% for each [45–48]).

Advanced age and comorbidity [36, 49, 50], aortic valve involvement [40, 51–53], and left-side [50, 54] and prosthetic valve IE disease [3] have all been associated with increased mortality rates. Persistent bacteremia, major emboli, mental status impairment or neurologic complications [50, 55, 56], and renal insufficiency [57] are all associated with adverse outcomes.

COMPLICATIONS OF IE

In a recent series of 287 patients with IE, more than two-thirds had a serious complication during treatment [58].

Fever. Among 123 patients with IE, >50% had defervesced within 72 h of beginning therapy; 72% and 84% were afebrile by the end of weeks 1 and 2 of therapy, respectively (figure 1) [59]. A duration of fever of >1 week after initiation of treatment and recurrent fever have both been associated with extensive cardiac infection, embolic phenomena,

Table 1. Summary of major prospective trials of short-course antibiotic therapy for uncomplicated viridans streptococcal infective endocarditis, by inpatient or outpatient status of patients.

Reference	No. of assessable patients	No. (%) of patients treated as inpatients and then as outpatients[a]	No. of inpatient days per patient	No. (%) of patients treated entirely on an outpatient basis
[25]	27	20 (76)	8 (average)	7 (23)
[26]	55	23 (39)	<7, 4% patients; 8–14, 25% patients; >15, 58% patients	7 (13)
[27]	48	43 (90)	Unknown (82% of all patient-days were for inpatients)[b]	5 (10)
[28]	51	Unknown	8 (CTX monotherapy); 14.5 (CTX-Gm)	Unknown

NOTE. CTX, ceftriaxone; Gm, gentamicin.

[a] Treated in the hospital, then iv therapy completed as outpatients.

[b] Of 672 days of antibiotic therapy (48 patients for 14 days), 124 days involved outpatients (~18%).

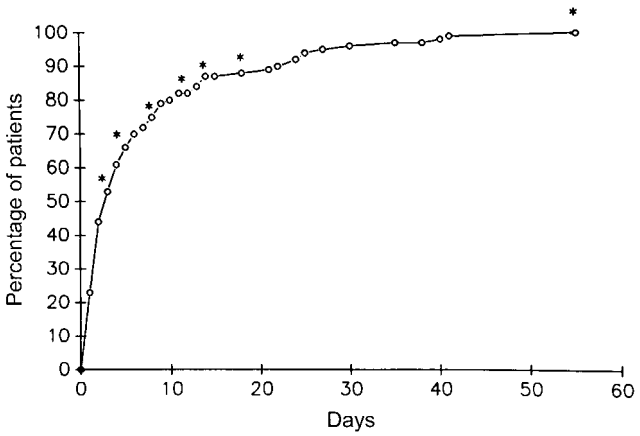

Figure 1. Timing of fever in 123 patients with infective endocarditis in a Kaplan-Meier plot that shows cumulative frequency of defervescence. Day of death for patients who died without becoming afebrile is shown by an asterisk. Reproduced with permission from Lederman et al. [59].

and drug hypersensitivity [59–62]. Of importance, resolution of fever may signify clearing of bacteremia but not sterilization of vegetations [62].

Heart failure. Heart failure due to valvular insufficiency is the leading complication of IE; it occurs in ⩽15%–65% of cases [40, 52, 53, 63]. Severe heart failure with frank pulmonary edema and cardiogenic shock is more common in patients with aortic insufficiency [40], *S. aureus* infection [35, 37, 41], and acute disease [35, 37, 41]. Echocardiography is an excellent tool for assessing valvular insufficiency and myocardial function. However, echocardiographic evidence of valvular regurgitation does not necessarily predict future course of IE; similarly, its absence does not ensure a good prognosis [64]. Rates of heart failure increase dramatically during the first month after a patient receives antibiotic therapy for IE [40, 63]. Rates of heart failure plateau at 6 months after initiation of therapy for patients with aortic valve disease and at 2 years after therapy for patients with mitral valve disease (figure 2) [40].

Emboli. Embolic events are the second most common complication of IE; they occur in 22%–43% of cases [65, 66].

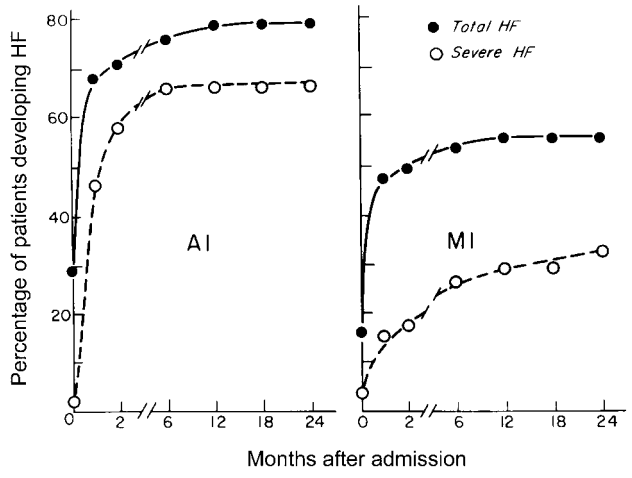

Figure 2. Timing of heart failure (HF) in patients who have infective endocarditis and aortic insufficiency (AI) or mitral insufficiency (AI). Cumulative percentages were computed by time-table method. Reproduced with permission from Mills et al. [40].

No host risk factors for embolization have been identified, and rates of embolization due to aortic valve vegetations are similar to those of mitral valve vegetations [66]. However, embolization rates are organism-specific; the rates for *S. aureus* IE are 2.4-fold greater than those for viridans streptococcal IE [66]. Other virulent organisms, HACEK group organisms (including *Haemophilus parainfluenzae*), nutritionally variant streptococci, group B streptococci, yeast, and fungi have been associated with larger, more friable vegetations that appear to be more likely to embolize [37, 55, 56, 66, 67].

The role of echocardiography in predicting embolic complications is controversial. The absence of vegetations on transthoracic echocardiograms or transesophageal echocardiograms does not exclude the possibility of embolization, particularly in patients with acute IE, but vegetations >10 mm in diameter, particularly on the mitral valve, have been correlated with an increased risk of embolization in several studies [65, 68, 69]. Most embolic events occur before therapy or within several days after the initiation of antibiotic therapy [55, 56, 66, 67], and the rate of embolization decreases to background levels by the third week of therapy (figure 3) [66].

Myocardial abscess. Perivalvular extension of IE, including abscess or fistula tract formation, is a less common but ominous complication of IE. Perivalvular extension has been documented during surgery or autopsy in 6%–41% of patients with native valve IE [70]. In a series from the 1960–1970s, abscesses were seen in 20% of patients with acute IE [37], but the actual incidence in patients with IE who do not undergo surgery and who do not die is unknown. Patients with prosthetic valves are at greatest risk for this complication [71].

Unfortunately, clinical parameters have been insensitive predictors of perivalvular abscess [72–74]. Aortic valve IE is most consistently associated with perivalvular extension [39, 75, 76]—41% of

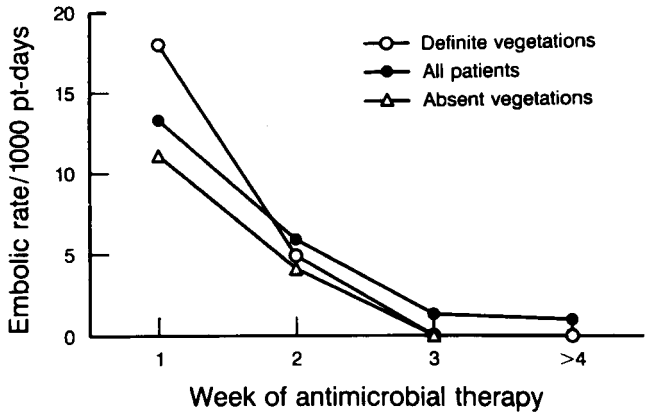

Figure 3. Timing and incidence of embolic events in patients with infective endocarditis. pt-days, Patient-days. Reproduced with permission from Steckelberg et al. [66].

cases involving the aortic valve versus 6% of cases involving the mitral valve in one autopsy series [39]. *S. aureus* is the pathogen most often associated with abscess [39, 77]. Other clinical features associated with periannular spread of IE have included new valvular regurgitation, pericarditis (usually a manifestation of ruptured valve ring abscess), new high-grade atrioventricular block, and a short fulminant clinical course [39]. Fever that persists for more than 1 week while the patient is receiving therapy and recurrent fever have been associated with abscess [60]. Evaluation for perivalvular extension is warranted for patients with persistent fever or bacteremia, new valvular murmur or insufficiency, recurrent emboli, or fixed conduction defects seen on electrocardiograms [70]. The sensitivity of electrocardiogram for perivalvular extension is only 27%–83% [70, 74, 78, 79], and the negative predictive value of a normal electrocardiogram is not known [70]. Transesophageal echocardiography has dramatically improved detection of perivalvular abscess, with a sensitivity of 87% and a specificity of 95%, compared with a sensitivity of 28% and a specificity of 99% for transthoracic echocardiography [80].

The interval between initiation of antibiotic therapy and detection of perivalvular abscess has not been well delineated. Of 27 patients who had valve ring abscesses discovered during autopsy, 3 (11%) had received no antibiotic therapy, 9 (33%) had received <10 days of therapy, and 15 (55%) had received >10 days of therapy [39]. In 2 cases, abscess was diagnosed 2 and 3 weeks after the blood had been sterilized [81]. In another series of 30 patients with a discharge diagnosis of perivalvular abscess who had undergone surgery for IE, the mean time between initiation of antibiotic therapy and surgery was 23 days (range, 1–180 days) [75].

PRINCIPLES IN THE APPLICATION OF OPAT

An important aspect of inpatient therapy for IE is careful observation. Complications of IE frequently occur after the start of treatment and are sufficiently common to require regular surveillance. Inpatient observation includes careful daily examination, and outpatient management should recreate the same standards of clinical follow-up. Existing OPAT guidelines recommend daily assessment of vital signs and physician visits at least once per week [30].

Tice [6, 23] has proposed several models for OPAT. In the physician-directed model, care is delivered in either the office or clinic by a coordinated team that includes doctors, nurses, and pharmacists. This optimal model maximizes the physician's opportunity to reinterview and examine the outpatient and to communicate with team members. In a home-infusion model, doctors order home antibiotic delivery and home nursing assessment. This model places patients at a distance from their doctors and care providers and, therefore, it may be an inferior option for management of IE. When a patient is not doing well on OPAT, ready access to the expert primary provider team may be life saving. In the aforementioned 2 patients from our consultative experience, there were delays in expert evaluation.

The quality of IE management was the subject of a recent study by Delahaye et al. [82] in France. The study demonstrated that there was variable compliance with prophylaxis and diagnostic guidelines and that surgery, even when clearly indicated, was often not pursued appropriately. An editorial that accompanied the study [83] suggested that the lack of adherence to guidelines may be due in part to the fact that individual physicians do not frequently treat patients with IE. More explicit criteria for the use of OPAT may help guide clinicians.

According to the American Heart Association Guidelines for IE treatment [10], "inpatient therapy does not prevent…and outpatient therapy does not increase" the risk of embolic complications during IE therapy. Our review suggests that the management of IE complications in the outpatient setting may indeed differ from management in the inpatient setting, which would result in different outcomes.

REVISED RECOMMENDATIONS FOR OPAT FOR IE

Until more data comparing hospital-based therapy with home-based therapy for IE become available, we propose being more selective in the use of OPAT for IE (table 2) [11, 20–24, 30, 31]. Our recommendations build on existing practice guidelines for administration of com-

Table 2. Proposed guidelines for the use of inpatient antibiotic therapy (IPAT) and outpatient parenteral antibiotic therapy (OPAT) for infective endocarditis (IE).

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	Complications of IE occur most frequently during this phase, and timely diagnosis is important for achieving optimal outcome.
	Preferred management: IPAT for 2 weeks.
	Exceptions: OPAT can be considered at 1 week for patients who meet the following 3 criteria: (1) infection with viridans streptococcal IE[a]; (2) medically stable condition without fever and with negative blood culture results, and stable electrocardiogram at time of proposed discharge; (3) no complications of IE and not in high-risk subgroup (see below).
Continuation phase (weeks 2–4 or 2–6)	Most patients who have not suffered complications of IE are likely to remain stable during the remainder of therapy, but side effects of parenteral antibiotic therapy may still occur.
	Preferred management: OPAT can be considered for the majority of patients who are medically stable (see above).
	Exceptions: IPAT should generally be continued for patients with any of the following characteristics: (1) complications of IE, such as congestive heart failure, conduction abnormality, mental status change, or evidence of perivalvular abscess on a transesophageal echocardiogram; (2) members of a high-risk subgroup: acute IE, aortic valve disease, prosthetic valve disease, or IE caused by *Staphylococcus aureus* or other virulent organisms.[b]
Essential elements of OPAT therapy	Patients should be educated and fully informed about the complications of IE and indications for and method of contacting their physician or IE care team.
	Patients and family should be reliable, compliant, and live close to the hospital.
	Routine postdischarge evaluation should include biweekly office or IE care team home visits during OPAT. Same-day evaluation by a member of the IE care team should be available for patients with recurrent fever or new symptoms.

[a] Expert consultation on individual patients may identify other low-virulence, low-risk organisms for which a similar approach may be taken.
[b] *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Neisseria gonorrhoeae,* beta streptococci, gram-negative bacteria, and fungi.

munity-based parenteral anti-infective therapy [11], on Rehm's [30] review, and on our own experience. Previous guidelines have focused on patient inclusion for OPAT (mainly those patients with sensitive streptococcal IE) and have cited gross contraindications to OPAT, including unstable hemodynamics, sepsis or ongoing bacteremia, poorly controlled congestive heart failure, new conduction abnormalities, vegetations of >10 mm in diameter, and neurologic signs and symptoms [11, 24]. We propose that additional attention be paid to the timing of IE complications, as justified in this review, and to more subtle disease features to guide patient exclusion.

Although the timing of some complications deserves more detailed study, the first 2 weeks of therapy appear to be the critical period of risk for most patients with treatable complications. Therefore, inpatient therapy or daily outpatient physician assessment should be considered standard for the majority of patients during this period (table 2). This interval is also in keeping with the current anticipated inpatient duration of stay of 13.1 days, as was noted earlier, and the data presented in table 1. Contraindications to OPAT during this critical phase would include congestive heart failure, conduction abnormalities, mental status changes, evidence of perivalvular abscess on transesophageal echocardiograms, or other serious complications of IE. Similarly, patients in high-risk subgroups, including patients with acute IE (as opposed to subacute), aortic valve disease, prosthetic valve IE, or IE caused by *S. aureus* or other virulent organisms, should not be routinely considered for OPAT during the critical phase. Until further data are available, relative contraindications to OPAT should be given extra weight for elderly patients and patients with concurrent medical problems.

During weeks 2–4 or 2–6 (i.e., the continuation phase of therapy), OPAT may be considered for the majority of patients. For consideration, patients should be free of systemic symptoms and should have negative blood culture results and a stable electrocardiogram. Patients with the aforementioned complications of IE and patients in high-risk subgroups may warrant continued care in an inpatient setting.

Although the appropriate duration of IE therapy in the inpatient setting can be debated, the fact that home therapy for IE requires particular vigilance is not a matter of debate [11, 30]. Nonetheless, our experience suggests that appropriate systems of health care for patients with IE in the outpatient setting may not be uniformly in place. Hospital and clinics need to establish outpatient infusion suites with staff knowledgeable about IE and its complications. Any recurrence of fever, symptoms of arrhythmia or cardiac failure, or neurologic symptoms should prompt same-day evaluation. In order to prevent patients with IE who are receiving OPAT from attending a foreign ur-

gent care or emergency setting for their antibiotic infusion, these outpatient infusion sites should have the capacity to administer treatments 7 days per week and have regular contact with the primary IE treatment team. If a home care model is used for infusion, patients should be seen frequently by their regular provider—as often as daily, during the first few weeks of the illness [11, 30], and then weekly—because this provider is uniquely able to assess subtle changes in their course.

In summary, we recommend a cautious approach to OPAT for patients with IE, with more attention to timing of hospital discharge and to patient exclusions. OPAT can be a desirable option for patients and providers if it is used carefully and selectively. Doctors should educate patients about the potential benefits and risks of OPAT, about the dynamic nature of IE, and about the symptoms that warrant immediate reevaluation. A fail-safe system for communication with and expert reevaluation by the physician or experienced IE team member should be established for each patient. Each organization should institute quality-assurance procedures for OPAT delivery, including outcome measures. Clinical researchers should attempt to develop more precise methods for predicting the risk and timing of complications of IE. Health policy makers should ensure that guidelines regarding OPAT for IE reflect the complexity and severity of this disease and that they do not encourage premature hospital discharge.

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