Repeat Infective Endocarditis: Differentiating Relapse from Reinfection

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Repeat infective endocarditis due to the same species can represent relapse of the initial infection or a new infection. We used time-based clinical criteria and pulsed-field gel electrophoresis–based molecular criteria to classify 13 cases of repeat infective endocarditis as either relapse or reinfection. The agreement between clinical and molecular criteria was imperfect (agreement in 10 [77%] of 13 cases).

Although most cases of infective endocarditis (IE) can be cured with either medical therapy or combined medical and surgical therapy, patients who recover remain at risk for an additional episode of IE. The lifetime risk of a second episode of IE among survivors of IE has been estimated to be between 2% and 22% [1–9]. When the same species is isolated during a subsequent episode of IE, there is often uncertainty as to whether the repeat infection is a relapse of the initial infection or a new infection.

Typically, in infectious diseases, the term “relapse” suggests an incompletely treated primary episode that results in the emergence of the original microorganism from a protected source (such as deep-tissue infection or seeded prosthetic hardware) [10, 11]. In contrast, the term “reinfection” is primarily used to describe infection with a new microorganism [10, 11]. For additional episodes of IE, investigators and clinicians have not consistently differentiated relapse from reinfection [1–9].

Traditionally, the timing of the subsequent episode of IE has been used to distinguish relapse from reinfection. Investigators and clinicians have presumed that an episode of IE caused by the same species within 6 months after the initial episode represents a relapse, whereas IE caused by the same species >6 months after treatment of the initial episode represents reinfection (historically referred to as “recurrent IE”) [1, 2, 4, 7, 8]. However, the accuracy of this 6-month threshold has not been rigorously examined using modern molecular methodology. The objective of this investigation was to use molecular fingerprinting to re-examine the traditional definitions of relapse and reinfection in patients with additional episodes of IE.

Methods. Patients with definite or possible IE according to the Duke criteria [12, 13] were identified at Duke University Medical Center (Durham, NC) between January 1986 and January 2004. Before April 1996, cases were identified retrospectively by review of microbiology laboratory records. After April 1996, cases were identified prospectively and were entered into the Duke Endocarditis Database, a registry of consecutive IE cases. Patients were included in this investigation if they had ≥2 episodes of IE during the study period, at least 1 of which was classified as definite IE. For patients with >2 episodes of IE, the first and second episodes were included in this analysis, except for 1 patient, for whom the first and third episodes were analyzed because the isolate from the second episode was not available for molecular analysis.

Blood cultures were processed in accordance with standard practice. Isolates were frozen and stored at −70°C. Antimicrobial susceptibility testing was interpreted in accordance with the recommendations of the NCCLS [14].

Molecular analysis was performed on all isolates pertaining to episodes of IE where a microorganism of the same species caused the initial episode and the subsequent episode. For strain typing, we performed macrochromosomal PFGE restriction fragment–length polymorphism analysis on available isolates, with an Smal endonuclease digestion, followed by electrophoresis in 1% agarose on a CHEF Mapper system (Bio-Rad Laboratories). Strain characterization among PFGE patterns was determined visually by the method of Tenover et al. [15]. Isolates were considered to be the same strain if their restriction patterns were indistinguishable (i.e., they had the same number of bands, and the respective bands were of the same size) or were very closely related (i.e., they had only a 1-band difference).

Patients with at least 2 episodes of IE were clinically classified as follows. An additional episode of IE caused by a microorganism of the same species within 6 months after the initial episode was classified as a relapse. An additional episode of IE caused by a microorganism of the same species >6 months after the initial episode was classified as reinfection. All additional
episodes caused by microorganisms of species different from the one that caused the initial episode were classified as reinfection, regardless of the time interval.

Patients with at least 2 episodes of IE were also classified on the basis of the results of PFGE analysis. For this investigation, we used the following molecular definitions. A confirmed relapse was defined as an additional episode of IE caused by a microorganism with an identical fingerprint to that of the isolate that caused the initial episode. Confirmed reinfection was defined as an additional episode of IE that was caused by a microorganism of a different species or an isolate of the same species that had a nonidentical PFGE pattern.

Results. Of the 428 patients in our prospectively ascertained cohort of patients who had IE, 20 (4.7%) had a repeat episode(s). Among all patients (including the retrospective cohort), 25 patients were identified with ≥2 episodes of IE. Of these 25 patients, 21 had 2 episodes of IE, and 4 had 3 episodes. The patients were primarily (64%) male, and the median age was 51 years (25th–75th percentile, 42–64 years). Comorbid conditions included hemodialysis (13 patients [52%]), injection drug use (2 [8.0%]), rheumatic and/or degenerative heart disease (5 [20%]), or congenital heart disease (2 [8.0%]). Infections primarily occurred on a native valve (76% of initial episodes and 60% of repeat episodes). The majority of the 50 IE episodes were caused by Staphylococcus aureus (10 [40%] of the initial episodes; 13 [52%] of the repeat episodes) and Enterococcus faecalis (4 [16%] of the initial episodes; 4 [16%] of the repeat episodes). The median time between the initial episode and repeat episode of IE was 9.1 months (25th–75th percentile, 3.8–24 months; range, 2.1–64 months).

In 13 patients, the infecting microorganism in the initial episode and the repeat episode of IE was the same species. By use of molecular criteria, 9 patients had a confirmed relapse, and 4 patients had a confirmed reinfection (table 1 and figure 1). Three patients were classified differently with the use of the 6-month–threshold clinical definition. Thus, the agreement between the molecular definition and the 6-month–threshold clinical definition was 10 (77%) of 13 cases. The agreement between the molecular definition and the 3-month–threshold clinical definition was 8 (62%) of 13 cases. With the use of molecular criteria, the median time between the initial and the subsequent episode of IE was shorter for patients with a confirmed relapse (2.9 months; 25th–75th percentile, 2.7–5.0 months; range, 2.1–9.1 months) than for patients with a confirmed reinfection (19 months; 25th–75th percentile, 5.7–33 months; range, 2.5–64 months).

Discussion. The nomenclature used to define additional episodes of IE has been hindered by inconsistent and imprecise definitions. Other authors have used clinical definitions based on the time between the first and second episodes of IE. Both a 6-month threshold [1, 2, 4, 7, 8] and a 3-month threshold [5, 9] have been used to distinguish relapse from reinfection. However, none of these investigations used molecular methods to distinguish relapse from reinfection with a different strain of the same species. Using molecular fingerprinting, we were able to assess the reliability of time-dependent clinical definitions. Although our data suggest that a clinical definition of relapse based on a 6-month threshold correlates better with molecular analyses than does a definition based on a 3-month threshold, neither has the discriminatory power of PFGE.

The proper diagnosis of additional episodes of IE has important implications. A diagnosis of relapsed IE suggests failed therapy and mandates a search for a persistent focus of infection (e.g., a valve-ring abscess), a longer course of treatment, or surgical therapy. In addition, a relapse of IE may differ in prognosis from a new episode. Lastly, for cases of repeat IE that are brought to medical-legal attention, accurate differentiation between relapse and reinfection would be imperative.

Figure 1. Results of PFGE performed on causative isolates for patients with an additional episode of infective endocarditis due to a microorganism of the same species. A through M refer to patients listed in table 1.
Table 1. Comparison of clinical and molecular definitions for 13 patients who had repeat episodes of infective endocarditis (IE) due to the same species as the initial episode.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Microorganism</th>
<th>Predisposing comorbidity</th>
<th>Time between episodes, months</th>
<th>Clinical definitiona</th>
<th>Molecular definitionb</th>
<th>Surgical treatment of initial episode of IE</th>
<th>Outcomec</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MSSA</td>
<td>Hemodialysis</td>
<td>5.0</td>
<td>Relapse</td>
<td>Confirmed relapse</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>B</td>
<td>MSSA</td>
<td>Hemodialysis</td>
<td>9.1</td>
<td>Reinfectiond</td>
<td>Confirmed relapsed</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>C</td>
<td>MSSA</td>
<td>Hemodialysis</td>
<td>17</td>
<td>Reinfection</td>
<td>Confirmed reinfection</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>D</td>
<td>MRSA</td>
<td>None</td>
<td>2.1</td>
<td>Relapse</td>
<td>Confirmed relapse</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td>E</td>
<td>MRSA</td>
<td>None</td>
<td>2.4</td>
<td>Relapse</td>
<td>Confirmed relapse</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td>F</td>
<td>MRSA</td>
<td>Hemodialysis</td>
<td>2.8</td>
<td>Relapse</td>
<td>Confirmed relapse</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>G</td>
<td>MRSA</td>
<td>Hemodialysis</td>
<td>4.0</td>
<td>Relapse</td>
<td>Confirmed relapse</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>H</td>
<td>MRSA</td>
<td>Hemodialysis</td>
<td>31</td>
<td>Reinfection</td>
<td>Confirmed reinfection</td>
<td>Yes</td>
<td>Survived</td>
</tr>
<tr>
<td>I</td>
<td>Staphylococcus epidermidis</td>
<td>None</td>
<td>2.5</td>
<td>Relapse</td>
<td>Confirmed reinfection</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>J</td>
<td>Enterococcus faecalis</td>
<td>None</td>
<td>2.7</td>
<td>Relapse</td>
<td>Confirmed relapse</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>K</td>
<td>E. faecalis</td>
<td>None</td>
<td>2.9</td>
<td>Relapse</td>
<td>Confirmed relapse</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>L</td>
<td>Propionibacterium acnes</td>
<td>Congenital heart disease</td>
<td>24</td>
<td>Reinfectiond</td>
<td>Confirmed relapsed</td>
<td>No</td>
<td>Survived</td>
</tr>
<tr>
<td>M</td>
<td>Streptococcus sanguis</td>
<td>Congenital heart disease</td>
<td>64</td>
<td>Reinfection</td>
<td>Confirmed reinfection</td>
<td>No</td>
<td>Survived</td>
</tr>
</tbody>
</table>

NOTE. MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible S. aureus.

a Based on a 6-month threshold.
b Based on PFGE analysis.
c Discharge status after the repeat episode of IE.
d Results discordant between clinical and molecular definitions.

We believe that PFGE or other molecular strain-typing methodology should be used whenever possible to evaluate repeat episodes of IE due to microorganisms of the same species. We propose the use of the following definitions.

**Confirmed relapse:** a repeat episode of IE that is shown by molecular analysis to be caused by the same microorganism as the previous episode.

**Confirmed reinfection:** a repeat episode of IE that is caused by a different species or is caused by a microorganism of the same species that is shown by molecular analysis to be a different strain.

**Possible relapse:** a repeat episode of IE caused by a microorganism of the same species for which confirmatory testing by molecular analysis has not been performed.

There are several limitations to this study. We recognize that one cannot exclude the possibility of a reinfection (as opposed to a relapse) with the same microorganism in patients who have an additional episode of IE due to a microorganism with an identical PFGE pattern. For example, reinfection of a hypothetical patient with a persistent colonizing strain of *S. aureus* could give the erroneous impression of relapse. Also, there is the possibility of an episode of IE being polyvalent but involving a single species, as has been reported for *Staphylococcus epidermidis* [16]. Our results are subject to referral bias, because the data were derived from a single tertiary care center. Some of the data (5 episodes that occurred before 1996) were collected retrospectively. Although comparable to previous studies, this study is limited by the small sample size. Finally, our estimation of the incidence of repeat IE is limited by the inability to ensure follow-up for patients readmitted to other institutions.

Clinicians should be aware of the limitations and uncertainty that result when purely clinical definitions of relapse and reinfection are used. Although the time between episodes is shorter for relapse than for reinfection, errors arise when 3- and 6-month thresholds are used for classification. Thus, when an additional episode of IE involving an isolate of the same species occurs, we believe that molecular strain-typing should be employed. We recognize that, in many cases, it is not possible to use molecular methods, because both isolates may not be available to confirm relapse versus reinfection. In such cases, we recommend using the term “possible relapse” or simply “repeat IE.”

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