Repeat endocarditis: analysis of risk factors based on the International Collaboration on Endocarditis – Prospective Cohort Study

L. Alagna[1], L. P. Park[2], B. P. Nicholson[3], A. J. Keiger[2], J. Strahilevitz[4], A. Morris[5], D. Wray[6], D. Gordon[7], F. Delahaye[8], J. Edathodu[9], J. M. Miró[10], N. Fernández-Hidalgo[11], F. M. Nacinovich[12], R. Shahid[13], C. W. Woods[2], M. J. Joyce[2], D. J. Sexton[14] and V. H. Chu[14]

1) *Department of Infectious Diseases, IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milan, Italy,* 2) *Division of Infectious Diseases and Microbiology, Durham VA Medical Center,* 3) *Institute for Medical Research, Durham, NC, USA,* 4) *Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University, Jerusalem, Israel,* 5) *Clinical Microbiology Laboratory, Auckland City Hospital, Auckland, New Zealand,* 6) *Department of Internal Medicine/Division of Infectious Disease and Pediatrics/Division of Infectious Diseases, Medical University of South Carolina, Charleston, SC, USA,* 7) *SA Pathology Microbiology and Infectious Diseases, Flinders Medical Centre, Adelaide, Australia,* 8) *Hopital Louis Pradel, Lyon-Bron, France,* 9) *Section of Infectious Diseases, Department of Medicine, King Faisal Hospital and Research Centre, Riyadh, Saudi Arabia,* 10) *Infectious Diseases Service, Hospital Clinic – IDIBAPS, University of Barcelona,* 11) *Department of Infectious Diseases, Hospital Universitari Vall d'Hebron, Barcelona, Spain,* 12) *Infectious Diseases Service, Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina,* 13) *Department of Medicine/GI and* 14) *Division of Infectious Diseases, Duke University Medical Center, Durham, NC, USA*

Abstract

Repeat episodes of infective endocarditis (IE) can occur in patients who survive an initial episode. We analysed risk factors and 1-year mortality of patients with repeat IE. We considered 1874 patients enrolled in the International Collaboration on Endocarditis – Prospective Cohort Study between January 2000 and December 2006 (ICE-PCS) who had definite native or prosthetic valve IE and 1-year follow-up. Multivariable analysis was used to determine risk factors for repeat IE and 1-year mortality. Of 1874 patients, 1783 (95.2%) had single-episode IE and 91 (4.8%) had repeat IE: 74/91 (81%) with new infection and 17/91 (19%) with presumed relapse. On bivariate analysis, repeat IE was associated with haemodialysis (p 0.002), HIV (p 0.009), injection drug use (IDU) ($p < 0.001$), *Staphylococcus aureus* IE (p 0.003), healthcare acquisition (p 0.006) and previous IE before ICE enrolment (p 0.001). On adjusted analysis, independent risk factors were haemodialysis (OR, 2.5; 95% CI, 1.2–5.3), IDU (OR, 2.9; 95% CI, 1.6–5.4), previous IE (OR, 2.8; 95% CI, 1.5–5.1) and living in the North American region (OR, 1.9; 95% CI, 1.1–3.4). Patients with repeat IE had higher 1-year mortality than those with single-episode IE (p 0.003). Repeat IE is associated with IDU, previous IE and haemodialysis. Clinicians should be aware of these risk factors in order to recognize patients who are at risk of repeat IE.

Keywords: Complication of endocarditis, recurrence of endocarditis, relapse of endocarditis, repeat endocarditis, risk factors for endocarditis
Original Submission: 25 April 2013; **Revised Submission:** 14 August 2013; **Accepted:** 12 September 2013
Editor: D. Raoult
Article published online: 11 November 2013
Clin Microbiol Infect 2014; **20:** 566–575
doi: 10.1111/1469-0691.12395

Corresponding authors: L. Alagna, Department of Infectious Diseases, Ospedale San Raffaele - Centro San Luigi; Università Vita-Salute San Raffaele, Via Stamira d'Ancona 20, 20147 Milano, Italy
E-mails: laura.alagna@gmail.com; **alagna.laura@hsr.it**
and
V. H. Chu, Division of Infectious Diseases, Duke University Medical Center, Box 102359, Durham, NC 27710, USA
E-mail: vivian.chu@duke.edu

A list of the ICE investigators appears in the Appendix.

Background

Repeat infective endocarditis (IE) is a major complication that can occur in patients who have recovered from an initial episode [1–3]. The lifetime rate of recurrent or 'repeat IE' (terminology proposed by this group [4]) is estimated to be between 2% and 31% [5–7]. Previous studies have identified risk factors for repeat IE such as intravenous drug use (IDU)

[1,6,8], congenital and rheumatic heart disease [6–8], prior episode(s) of endocarditis [5], chronic dialysis [2], male gender and increasing of age (>65 years) [9]. Among patients who undergo surgical treatment for IE, prosthetic valve endocarditis, positive valve culture at surgery and persistence of fever at the seventh postoperative day have been shown to be predictive of repeat IE [10]. The interpretation of these findings, however, is limited by inconsistent definitions of repeat IE, in general, and inconsistent definitions of relapse vs. re-infection among patients who have a repeat episode of IE due to the same bacterial species as the initial episode.

Among patients who experience a repeat episode of IE due to the same bacterial species, molecular methods, such as PFGE, can be used to differentiate relapse from re-infection [4]. Nevertheless, molecular methods are usually impractical in the clinical setting and therefore the time-interval between IE episodes is typically used to distinguish between relapse and re-infection. For example, an episode of IE caused by the same species within 6 months of the initial episode would be considered a relapse, while an episode of IE caused by the same species >6 months from the initial episode would be considered a re-infection [4,6,8,9,11]. Both 3-month and 6-month time-interval-based definitions have been used. This group found an agreement of 77% between the 6-month time-interval-based classification and the molecular-based classification in a small, well-defined cohort [4].

The epidemiology of IE has shifted such that healthcare-associated infections [12,13] and infections in older populations, with a higher median age at IE onset [14], feature prominently. With these changes a better contemporary understanding of the incidence and risk factors for repeat IE is needed [14–16]. The purpose of this study was to describe the clinical characteristics, identify risk factors and examine 1-year mortality of patients with repeat IE in a large, contemporary cohort.

Methods

ICE – PCS

This analysis is based on the International Collaboration on Endocarditis – Prospective Cohort Study (ICE – PCS), a prospective, multicentre database of patients with IE. From January 2000 to September 2006, 5594 patients with possible or definite endocarditis according to the Duke criteria [17,18] were enrolled. The ICE – PCS database consists of data from 64 sites, in 28 countries worldwide. Details regarding patient enrollment have been previously reported [16].

Definitions

Presumed IE relapse was defined as a new episode caused by the same bacterial species, within 6 months of the first episode. Presumed new infection was defined as a new IE episode caused by a different bacterial species or by the same bacterial species >6 months from the initial episode [4,6,8,9,11]. We defined the interval between IE episodes as the number of days between the dates of admission for IE or the date of IE-related fever onset if it was hospital-acquired. We included new IE cases occurring at least 10 weeks from the initial episode. This threshold was chosen arbitrarily as we assumed that 4 weeks beyond a 6-week treatment course would be a reasonable interval for having a new IE episode not related to suboptimal treatment of the initial infection.

Community-acquired IE was defined as signs or symptoms of IE developing before hospitalization in a patient without extensive out-of-hospital healthcare contact. Nosocomial healthcare-associated IE was defined as IE occurring in a patient hospitalized for more than 48 h. Non-nosocomial healthcare-associated IE was defined as the diagnosis of IE within 48 h of admission specifically in patients who, before the onset of IE: (i) received intravenous therapy or specialized nursing care within 30 days; (ii) received haemodialysis; (iii) were hospitalized for at least 2 days in the preceding 90 days, or (iv) resided in a long-term care facility [15,16].

Patient selection

Patients from the ICE – PCS with a diagnosis of definite IE on a native or prosthetic valve and with 1-year follow-up were considered (Fig. 1). We excluded patients who had missing data at 1-year follow-up (2521/5594, 45%). We also excluded patients with intra-cardiac lead IE (n = 270), because a repeat episode of IE could be related to a retained device [19,20] and patients (n = 49) who lacked information on type of IE (e.g. native vs. prosthetic vs. intra-cardiac lead).

We distinguished patients with only one episode of IE ('single-episode' IE) from those with more than one episode ('repeat' IE) and we distinguished presumed relapse from presumed new infection [4,6,8,9,11]. Among 174 patients with repeat IE, only patients with documented definite IE for both episodes were included (Fig. 1).

We excluded the following patients: 71 (41%) with insufficient data to validate a repeat IE episode; eight (0.4%) with a bacterial culture negative for the suspected second episode because it was impossible to differentiate between relapse and new infection due to the patients' complex medical history; and four (0.2%) with the relapse episode within 10 weeks of the first one. We made two exceptions with the 10-week repeat IE criteria: (i) a patient with a second episode 58 days after the initial episode because a complete recovery was documented, clinically and by