Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study

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Abstract

Enterococci are reportedly the third most common group of endocarditis-causing pathogens but data on enterococcal infective endocarditis (IE) are limited. The aim of this study was to analyse the characteristics and prognostic factors of enterococcal IE within the International Collaboration on Endocarditis. In this multicentre, prospective observational cohort study of 4974 adults with definite IE recorded from June 2000 to September 2006, 500 patients had enterococcal IE. Their characteristics were described and compared with those of oral and group D streptococcal IE. Prognostic factors for enterococcal IE were analysed using multivariable Cox regression models. The patients' mean age was 65 years and 361/500 were male. Twenty-three per cent (117/500) of cases were healthcare related. Enterococcal IE were more frequent than oral and group D streptococcal IE in North America. The 1-year mortality rate was 28.9% (144/500). *E. faecalis* accounted for 90% (453/500) of enterococcal IE. Resistance to vancomycin was observed in 12 strains, eight of which were observed in North America, where they accounted for 10% (8/79) of enterococcal strains, and was more frequent in *E. faecium* than in *E. faecalis* (3/16 vs. 7/364 , p 0.01). Variables significantly associated with 1-year mortality were heart failure (HR 2.4, 95% CI 1.7—3.5, p <0.0001), stroke (HR 1.9, 95% CI 1.3—2.8, p 0.001) and age (HR 1.02 per 1-year increment, 95% CI 1.01—1.04, p 0.002). Surgery was not associated with better outcome. Enterococci are an important cause of IE, with a high mortality rate. Healthcare association and vancomycin resistance are common in particular in North America.

Keywords: *Enteroccoccus faecalis*, healthcare-associated infection, infective endocarditis, prognosis, vancomycin resistance
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Introduction

Enterococci are reportedly the third most common group of endocarditis-causing pathogens after streptococci and staphylococci. A few, relatively small, case series of enterococcal infective endocarditis (IE) have been published [1–9]. Based on these studies, the most distinctive features of enterococcal IE are that they more frequently affect elderly and prosthetic valve patients [3,5,8], and are more often nosocomially acquired than other forms of IE [2,7]. Nosocomial acquisition appears to worsen outcome. The mortality rate is intermediate to that of streptococcal and staphylococcal IE [1,2,4,8]. Patients with prosthetic valve enterococcal IE are more likely to develop intracardiac abscesses and less likely to have detectable vegetations on echocardiography than patients with native valve enterococcal IE [3]. In contrast, native and

prosthetic valve enterococcal IE do not appear to differ in rate of complications, need for surgery or mortality [1].

To date, all but two [4,6] of these case series were collected retrospectively and some are more than 20 years old [9]. The aim of this study was to analyse the current characteristics and prognostic factors of enterococcal IE within the International Collaboration on Endocarditis – Prospective Cohort Study (ICE-PCS), which forms the largest series of IE ever collected prospectively.

Methods

International Collaboration on Endocarditis – Prospective Cohort Study

Data from the ICE-PCS were used for this study. The background and inclusion criteria of this prospective, multicentre, international registry of IE have been reported previously [10,11]. Between June 2000 and September 2006, 4794 patients from 64 centres in 28 countries were enrolled. The ICE-PCS database is maintained at the Duke Clinical Research Institute, the coordinating centre for ICE studies. Informed consent (oral/written) was obtained from all patients according to local institutional review boards or ethics committee guidelines at all sites.

Patient selection and data collection

Patients were identified prospectively using site-specific procedures to ensure consecutive enrollment. Patients were enrolled in the ICE-PCS if they met criteria for possible or definite IE based on the modified Duke criteria [12]. Only patients with definite IE were included in the current study. To preserve the assumption of independence of observations, only the first episode of IE recorded for an individual patient was used in the analysis.

The method of data collection for the ICE-PCS has been previously reported [11]. Briefly, all sites used a standard case report form to collect data. It included 275 variables and was developed by the ICE according to standard definitions. Data were collected during the index hospitalization and then entered at the coordinating centre or by site investigators using an Internet-based data entry system. Microbial species identifications were performed locally in each medical centre according to its own procedures. All sites obtained information on 1-year survival through the civil registry office, medical records and/or patient contact when necessary.

Definitions and case groups

Definitions of the variables included in the ICE-PCS case report form have been previously reported [11].

Community-acquired IE was defined as IE diagnosed at the admission time (or within the first 48 h) in a patient who did not fulfill the criteria for healthcare-associated infection. Healthcare-associated IE was defined as nosocomial IE or non-nosocomial healthcare-associated IE. Nosocomial IE was defined as IE that developed in a patient who was hospitalized for more than 48 h before the onset of signs or symptoms consistent with IE. Non-nosocomial healthcare-associated IE was defined as IE diagnosed within 48 h of admission in an outpatient with extensive healthcare contact, as reflected by any of the following criteria: (i) receipt of intravenous therapy, wound care or specialized nursing care at home within the 30 days before the onset of IE; (ii) attendance at a hospital or haemodialysis clinic or receipt of intravenous chemotherapy within the 30 days before the onset of IE; (iii) hospitalization in an acute care hospital for 2 or more days in the 90 days before the onset of IE; or (iv) residence in a nursing home or long-term care facility.

In an effort to group centres with geographical and sociodemographic similarities, five meta-regions were defined as follows: North America, South America, Northern Europe, Southern Europe/Middle East/Africa and Australia/New Zealand/Asia (see supporting data).

The group of enterococcal IE included all cases of IE due to *E. faecalis*, *E. faecium*, *E. durans*, *E. avium*, *E. casseliflavus* or *E. gallinarum*, as well as enterococci that could not be further identified to the species level. For comparative analyses, we formed two additional groups of IE, oral streptococci IE and group D streptococci IE. Table 1 shows the list of organisms that are included in these two groups. We did this because enterococci, oral and group D streptococci all belong to the *Streptococcaceae* family.

TABLE 1. List of pathogens included in the three groups of pathogens used for comparative analysis

Enterococci	*N*	Oral streptococci	*N*	Group D streptococci	*N*
E. faecalis	453	*S. mitis*	79	*S. bovis*[a]	270
E. faecium	19	*S. mutans*	64	*S. gallolyticus*	17
E. durans	6	*S. oralis*	42	*S. equinus*	2
E. casseliflavus	2	*S. sanguis*	31	*S. pasteurianus*	1
E. gallinarum	1	*S. salivarius*	23	Group D NIS[b]	3
Enterococci NIS[b]	19	*S. gordonii*	12		
		S. anginosus	17		
		S. constellatus	5		
		S. intermedius	5		
		S. milleri group NIS[b]	4		
		S. acidominimus	7		
		S. parasanguis	1		
		S. viridans NIS[b]	533		
TOTAL	500		823		293

[a]*S. bovis*' refers to the results of species identification according to the former, outdated classification of group D streptococci.
[b]Not identified to species level.