RESEARCH NOTE

Nosocomial infective endocarditis: should the definition be extended to 6 months after discharge

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ABSTRACT

Because the microbiology and patient population of infective endocarditis (IE) have evolved, the traditional definition of nosocomial IE may require revision. The question of whether this definition should be extended to 6 months after discharge was explored, and a high rate of episodes with nosocomial pathogens (coagulase-negative staphylococci) and a low rate of episodes with community pathogens (streptococci) in the extended nosocomial group were found. Therefore, modification of the traditional definition is proposed, distinguishing between early (as traditionally described) and late nosocomial IE (IE in association with a significant invasive procedure performed during a hospitalization between 8 weeks and 6 months before the onset of symptoms).

Keywords Community-acquired, definition, infective endocarditis, nosocomial

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Rates of nosocomial infective endocarditis (IE) in previous studies varied from 7% to 33% [1–4]. Recent series described cases of IE due to pathogens that were considered to be nosocomial, e.g. coagulase-negative staphylococci (CoNS), beyond the traditional 8-week period [3,5]. This study involved the current definition of nosocomial IE and whether it should be extended to 6 months after discharge.

Patients older than 16 years with a definite diagnosis of IE according to the modified Duke's criteria [6] between June 2000 and December 2006 were included. Nosocomial IE was defined as diagnosis of IE >72 h after admission to the hospital (tertiary-care and non-tertiary-care centre) or acquisition of IE in association with a significant invasive procedure performed during a recent hospitalization <8 weeks before the onset of symptoms [1,5]. Cases of healthcare-acquired IE, e.g. patients undergoing hemodialysis, were included in the nosocomial group, but patients who were residents of a nursing home were not. Extended nosocomial IE was defined as IE acquired in association with a significant invasive procedure performed during one or more recent hospitalizations (tertiary-care and non-tertiary-care centre) between 8 weeks and 6 months before the onset of symptoms. The 6-month limit to this definition was based on the observations of Ben Ami *et al.* [3]. Significant invasive procedures included urogenital procedures, gastrointestinal procedures, surgical intervention and central venous and arterial catheter placements [3,7]. Patients were treated according to the American Heart Association guidelines [8,9] and predefined indications for surgery [10].

Comparisons among patient groups were performed using chi-squared analysis or Fisher's exact test for categorical variables. The significance level used in univariate analysis was $p < 0.05$. All p-values were two-sided. Multiple comparisons were adjusted for using the Bonferroni correction. Statistical analysis was performed with the SPSS software package (version 15.0; Chicago, IL, USA).

Two hundred and seventy-two patients experienced 287 episodes of IE. Seventy-seven episodes (27%) were nosocomial IE according to the traditional definition, 35 episodes (12%) belonged to the extended nosocomial group, and the remaining 175 episodes (61%) were community-acquired IE. Staphylococci were the predominant microorganisms in 112 episodes (39%); 77 of these episodes involved *Staphylococcus aureus* and,

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among these, 18 involved methicillin-resistant *S. aureus*. Thirty-five episodes of IE (12%) were due to CoNS; 23 of these involved methicillin-resistant isolates. Streptococcal IE was observed in 83 episodes (29%), 49 of which involved viridans streptococci. Fifty-two episodes (18%) were caused by enterococci and 40 episodes (14%) by other microorganisms (including 28 cases of culture-negative IE and 12 cases due to rare or fastidious microorganisms). Enterococci were distributed nearly equally between the three groups. Table 1 summarizes the distribution of microorganisms and the type of invasive procedure according to the origin of IE. In the nosocomial and extended nosocomial group, the most frequent microorganisms involved were staphylococci, whereas in the community-acquired group, streptococci predominated. In the extended nosocomial group, six methicillin-susceptible *S. aureus* (MSSA) episodes were registered. The preceding procedures included placement of an orthopaedic prosthesis in two episodes, which were complicated by an MSSA sepsis in one episode and a wound infection due to MSSA in the other episode; the prosthesis and the wound were both considered to be the portal of entry. Neurosurgery was performed in one episode. Placement of a portacath was registered in one episode, followed by chemotherapy, and the catheter was considered to be the focus of bacteraemia. Replacement of a pacemaker occurred in one episode, but the portal of entry was probably an abscess on the thumb. One episode had no clear portal of entry, but metastatic infection (septic arthritis and osteomyelitis) occurred.

Table 1. Epidemiological and microbiological characteristics and the type of invasive procedure (nosocomial, extended nosocomial or community-acquired infective endocarditis)

Patient group	Nosocomial *n* = 77 (%)	Extended nosocomial *n* = 35 (%)	Community-acquired *n* = 175 (%)
Microbiology			
Staphylococcus aureus	28 (37)	7 (20)	42 (24[a])
MSSA	17 (22)	6 (17)	36 (21)
MRSA	12 (16)	1 (3)	5 (3[a])
CoNS	16 (21)	7 (20[b])	12 (7[a])
Streptococci	8 (11)	6 (17[b])	69 (39[a])
Enterococci	15 (20)	8 (23)	29 (17)
Other	9 (12)	7 (20)	24 (14)
Patient characteristics			
Age (years)	70	69	66[a]
Gender (male)	42 (55)	23 (66)	107 (61)
Native valve	37 (49[c])	28 (80)	115 (65[a])
Prosthetic valve	36 (47[c])	5 (14[b])	55 (31[a])
Other than native valve and prosthetic valve[d]	3 (4)	2 (6)	6 (3)
Type of procedure[e]			
Urogenital	Enterococci (3)	Enterococci (5), viridans streptococci (1)	CNE[f] (1)
Gastrointestinal	Enterococci (3), MSSA (2), CoNS (2), *S. bovis* (1), CNE[f] (1), *Candida* spp. (1)	*S. bovis* (2), *Escherichia coli* (1), CNE[f] (1)	*S. bovis* (2)
Catheter	CoNS (11), MRSA (10), MSSA (9), CNE[f] (7), enterococci (6), streptococci (3), *Aspergillus* spp. (1), *Candida* spp. (1)	CoNS (3), MSSA (2), viridans streptococci (3), enterococci (1), CNE[f] (1)	*S. bovis* (1)
Cardiac surgery	MRSA (8), MSSA (4), CoNS (4), CNE[f] (3), enterococci (3), *Candida* spp. (1)	CoNS (1)	
Orthopaedic surgery	MSSA (1), MRSA (1)	MSSA (2)	
Thoracic surgery	MSSA (1), MRSA (1)		
Vascular surgery	Enterococci (1)	MRSA (1), CoNS (1)	
Neurosurgery		MSSA (1)	
Soft tissue excision	MRSA (1), enterococci (1)	*E. coli* (1)	

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; CNE, culture-negative endocarditis.
[a]Community-acquired vs. nosocomial; $p < 0.05$.
[b]Extended nosocomial vs. community-acquired; $p < 0.05$.
[c]Nosocomial vs. extended nosocomial; $p < 0.05$.
[d]Other episodes included six pacemakers, two infected pseudo-aneurysms, superinfection of two Bentall aorta prostheses, and one case of ventricular wall involvement.
[e]Some episodes of IE were preceded by >1 invasive procedure.
[f]Culture-negative IE.

Table 2. Distributions of timing of onset of infective endocarditis caused by coagulase-negative staphylococci between cases involving native and prosthetic valves

Timing of onset	Prosthetic valve *n* = 19 (%)	Native valve *n* = 14 (%)
Nosocomial	11 (58)	4 (29)
Extended nosocomial	4 (21)	3 (21)
Community-acquired	4 (21)	7 (50)

Rates of infection with CoNS were similar between the nosocomial group and the extended nosocomial group (p 0.9) but were significantly higher in the extended nosocomial group than in the community-acquired group (p 0.01). Of the extended nosocomial CoNS episodes, 43% (3/7) involved native valves and 57% (4/7) prosthetic valves (p 1.0; Table 2). Rates of streptococcal infection were significantly higher in the community-acquired group than in the extended nosocomial group (p 0.01). In the extended nosocomial group, four episodes with viridans streptococci were observed and two with *Streptococcus bovis*. The preceding procedures in four episodes with viridans streptococci were a percutaneous coronary intervention in one episode, an implantable cardioverter defibrillator (ICD) implantation in one episode, a cardiac catheterization and an intravenous angiography in one episode, and an episiotomy in one episode. There were no previous specific dental procedures in these episodes. The preceding procedures in two episodes with *Streptococcus bovis* included a sigmoid resection due to a tubular adenoma in one episode and a gastroscopy and colonoscopy in the other episode.

This study aimed to reassess the definition of nosocomial IE and explore the probable nosocomial origin of IE in cases arising up to 6 months after discharge. The data document a high rate of hospital pathogens, e.g. CoNS, and a low rate of community pathogens, e.g. viridans streptococci, causing IE up to 6 months after an invasive procedure during hospitalization. Patients may become colonized during hospitalization by microorganisms (e.g. CoNS) associated with long incubation periods, resulting in the development of IE >8 weeks after hospitalization. Therefore, a reclassification of the definition of nosocomial IE is proposed, distinguishing between early IE (occurring more than 72 h after admission to the hospital or within 8 weeks after a significant invasive procedure performed during hospitalization) and late nosocomial IE (occurring between 8 weeks and 6 months after a significant invasive procedure performed during hospitalization). A clinically relevant consequence of the extension of the definition is that, for patients with suspected late nosocomial IE, initial therapy should include antimicrobial agents active against CoNS, irrespective of prosthetic or native valve IE. However, more epidemiological studies are required before drawing final conclusions about the extension of this definition of nosocomial IE to 6 months after discharge and, until then, the proposed definition should be used with caution.

Similar rates of enterococcal IE were observed in the three groups. These data suggest that nosocomial enterococcaemia may become a major criterion for IE as proposed previously for *S. aureus*. Currently, nosocomial enterococcaemia is only a minor criterion in the modified Duke criteria, in contrast to community-acquired enterococcaemia which is a major criterion [6].

TRANSPARENCY DECLARATION

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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RESEARCH NOTE

Evaluation of a new meropenem–EDTA double-ended Etest strip for the detection of the CfiA metallo-β-lactamase in clinical isolates of *Bacteroides fragilis*

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ABSTRACT

Thirty-five *Bacteroides fragilis* clinical isolates with varying susceptibility to meropenem were analysed with a prototype of a double-ended Etest strip containing meropenem ± EDTA, designed for the detection of the CfiA metallo-β-lactamase. Phenotypic results obtained with this new Etest strip were related to the genotype and compared to the results of the Etest containing imipenem ± EDTA. Whereas the Etest with imipenem ± EDTA only allowed detection of isolates with high-level resistance (both MICs of imipenem and meropenem >32 mg/L), reflecting the possible underestimation of CfiA prevalence in *B. fragilis*, the Etest with meropenem ± EDTA proved to be more accurate, particularly for isolates with low-level carbapenem resistance, suggesting its potential for broader detection of CfiA production.

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Bacteroides fragilis is an important anaerobic pathogen commonly associated with polymicrobial infections. Carbapenems are normally highly active against *B. fragilis.* However, carbapenem-resistant *B. fragilis* isolates have been reported [1–15], mainly because of the production of CfiA, a class B metallo-β-lactamase (MBL) present in up to 7% of those isolates [3,4]. This enzyme is usually poorly expressed, but the insertion of a variety of insertion sequence (IS) elements upstream of *cfiA*, subsequent to a single genetic event selected with carbapenems [11,16], switches on gene expression and leads to high-level carbapenem resistance [4,5,11–16]. Thus, it is important to detect all *B. fragilis* isolates that harbour the *cfiA* gene in order to avoid inappropriate carbapenem usage, which may result in the selection and emergence of high-level resistance in these strains. In that respect, enzymatic studies of CfiA [17] have shown that meropenem is a better substrate than imipenem for this MBL of *B. fragilis*.

The aim of this preliminary study was to assess the potential value of a novel Etest strip containing meropenem ± EDTA to detect carbapenem resistance due to CfiA in *B. fragilis.*

Thirty-five *B. fragilis* clinical isolates were examined. Seventeen of these, displaying either reduced susceptibility (MIC: >1 and ≤4 mg/L) or resistance (MIC: >8 mg/L) to meropenem, were obtained from different microbiology laboratories between 2005 and 2007 as part as of a multicentre survey [2]. Eighteen clinically relevant *B. fragilis* isolates susceptible to meropenem (MIC: <1 mg/L) were collected during 2005 at the