Clinical Features and Rate of Infective Endocarditis in Non-Faecalis and Non-faecium Enterococcal Bacteremia

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Non-faecalis and non-faecium enterococci are an occasional cause of bacteremia, and some cases of infective endocarditis caused by these pathogens have been reported. However, the rate of infective endocarditis in non-faecalis and non-faecium enterococcal bacteremia is still undetermined. We compared the clinical features and the rate of infective endocarditis of 70 cases of non-faecalis and non-faecium enterococcal bacteremia with those of 65 cases of Enterococcus faecalis bacteremia. Non-faecalis and non-faecium enterococcal bacteremia was more frequently associated with biliary tract infection and polymicrobial bacteremia, and was less frequently associated with infective endocarditis, than was E. faecalis bacteremia (57% vs. 28%, p < 0.01; 47% vs. 31%, p=0.05; 1% vs. 14%, p < 0.01, respectively).

Key Words: Enterococci; Bacteremia; vanC; Endocarditis

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INTRODUCTION

Enterococcus faecalis and Enterococcus faecium are significant human pathogens. Hence, the clinical features and outcomes of infections caused by these organisms have been well described. However, few clinical studies have been conducted on infections caused by non-faecalis and non-faecium enterococci such as Enterococcus avium, Enterococcus hirae, Enterococcus durans, Enterococcus gallinarum, Enterococcus casseliflavus, and Enterococcus flavescens, although these are also encountered as significant human pathogens. Among the non-faecalis and non-faecium enterococci, E. gallinarum, E. casseliflavus, and E. flavescens possessing the vanC gene are characterized by motility and intrinsic low-level resistance to vancomycin (the VanC phenotype). These species have caused concern, because treatment failure or inducible vancomycin resistance is possible during vancomycin therapy.

Enterococci are the third common etiologic agent of infective endocarditis, accounting for 11% of cases. E. faecalis is a common cause of infective endocarditis, and >3% of cases of E. faecalis bacteremia have infective endocarditis. In contrast, only <1% of cases of E. faecium bacteremia have infective endocarditis. Some cases of infective endocarditis caused by non-faecalis and non-faecium enterococci have also been reported. However, the rate of infective endocarditis in non-faecalis and non-faecium enterococcal bacteremia is still undetermined.

The aim of this study was to compare the clinical features and the rate of infective endocarditis of bacteremia due to non-faecalis and non-faecium enterococci with those of E. faecalis bacteremia.

MATERIALS AND METHODS

1. Patients
The electronic medical records of all patients with positive blood cultures for enterococci between January 1999 and August 2003 at Seoul National University Hospital (Seoul, Republic of Korea) were retrospectively reviewed. Underlying diseases, the primary site of bacteremia, co-morbid or predisposing conditions, antibiotic resistance, and treatment outcomes in patients with non-faecalis and non-faecium enterococcal bacteremia were compared with those in patients with E. faecalis bacteremia. Appropriate antibiotic treatment was defined as the use of one or more active antibiotics to which the organism was susceptible in vitro within 5 days of the date on which a positive blood culture was obtained. Antibiotics considered active included penicillin, ampicillin, piperacillin, vancomycin, teiclo-
nin, quinupristin-dalfopristin, and linezolid.15

2. Microbiological tests

*Enterococcus* species were identified on the basis of 6.5% NaCl tolerance, bile-esculin hydrolysis, and growth rate at 45°C. Species were identified from the results obtained with the Vitek system (bioMérieux, Marcy l’Etoile, France) and by tests for motility, yellow pigmentation, and methyl-α-D-glucopyranoside.16,17 Antibiotic susceptibilities were determined by the disk diffusion method, following the recommendations of the Clinical and Laboratory Standards Institute.18 The vancomycin and teicoplanin minimal inhibitory concentration (MIC) was determined by Etest® (AB BIODISK, Solna, Sweden) according to the manufacturer’s manual. VanC phenotype enterococci were defined as enterococcal isolates with intrinsic low-level resistance to vancomycin (MICs 2-32 μg/ml) and susceptibility to teicoplanin.19

3. Statistical analysis

Categorical variables were compared by using the Fisher’s exact test or the Pearson χ² test, as appropriate, and continuous variables were compared by using the Mann-Whitney test or Student’s t test. All tests of significance were 2-tailed, and p≤0.05 was considered to be significant. Statistical analyses of the data were performed by using SPSS for Windows (ver. 12.0; SPSS Inc., Chicago, IL).

RESULTS

1. *Enterococcus* species in blood isolates

We identified 292 cases with enterococcal bacteremia during the study period. One hundred fifty (51.4%) were caused by *E. faecium* and 65 (22.3%) by *E. faecalis*. Seventy (24.0%) were caused by non-faecalis and non-faecium enterococci; 23 (7.8%) by *E. avium*, 20 (6.8%) by *E. gallinarum*, 19 (6.5%) by *E. casseliflavus*, 7 (2.4%) by *E. hirae*, and 1 (0.3%) by *E. durans*. The species responsible for seven (2.4%) isolates could not be identified. The patients from whom the isolates could not be identified were excluded from the analysis. None of patients with non-faecalis and non-faecium enterococcal bacteremia were clustered in time or place of occurrence.

2. Clinical features and the rates of infective endocarditis in non-faecalis and non-faecium enterococcal bacteremia

The clinical features of 135 patients with bacteremia caused by non-faecalis and non-faecium enterococci or *E. faecalis* are shown in Table 1. Compared with cases of *E. faecalis* bacteremia, underlying biliary disease and biliary tract infections were significantly more common in cases of non-faecalis and non-faecium enterococcal bacteremia. Polymicrobial bacteremia was also more common in cases of non-faecalis and non-faecium enterococcal bacteremia. *E. coli* (n=11), *Pseudomonas* species (n=6), and *Klebsiella* species (n=4) were the predominant blood co-isolates from cases of non-faecalis and non-faecium enterococci. Valvular heart disease and infective endocarditis were significantly less common in non-faecalis and non-faecium enterococcal bacteremia than in *E. faecalis* bacteremia (Table 1). However, 14-day mortality was not significantly different between patients with non-faecalis and non-faecium enterococcal bacteremia and patients with *E. faecalis* bacteremia (16% vs. 15%, p=0.93; Table 2).

3. Clinical features of patients with vanC phenotype enterococci

We compared the clinical features, outcomes, and microbiological data for bacteremia caused by VanC phenotype enterococci with those of bacteremia caused by non-faecalis and non-faecium enterococci without the VanC phenotype (Table 3). Biliary tract infection was the most common infection site in both groups (48% vs. 64%). No significant differences were apparent in underlying disease, infection site, or other clinical characteristics between these two

| Variable                        | Non-faecalis and non-faecium enterococci (N=70) | *E. faecalis* (N=65) | p value |
|---------------------------------|-----------------------------------------------|---------------------|---------|
| Underlying disease              |                                               |                     |         |
| Benign biliary disease          | 37 (53)                                       | 12 (18)             | <0.01*  |
| Urologic disease                | 4 (6)                                         | 5 (8)               | 0.74    |
| Valvular heart disease          | 0 (0)                                         | 7 (11)              | <0.01*  |
| Primary site of infection       |                                               |                     |         |
| Biliary tract                   | 40 (57)                                       | 18 (28)             | <0.01*  |
| Urinary tract                   | 5 (7)                                         | 11 (17)             | 0.08    |
| Infective endocarditis          | 1 (1)                                         | 9 (14)              | <0.01*  |
| Comorbid or predisposing condition |                                               |                     |         |
| Polymicrobial                    | 33 (47)                                       | 20 (31)             | 0.05*   |
| Nosocomial                       | 38 (54)                                       | 36 (55)             | 0.90    |

*aStatistically significant, p≤0.05.

Table 1. Clinical features of 135 patients with bacteremia caused by non-faecalis and non-faecium enterococci or *E. faecalis*
TABLE 2. Antibiotic resistance and outcome of 135 patients with bacteremia caused by non-faecalis and non-faecium enterococci or *E. faecalis*

| Variable                              | Number (%) of patients with bacteremia caused by Non-faecalis and non-faecium enterococci (N=70) | E. faecalis (N=65) | p value |
|---------------------------------------|-------------------------------------------------------------------------------------------------|--------------------|---------|
| Antibiotic resistance                 |                                                                                                |                    |         |
| Ampicillin resistance                 | 17 (24)                                                                                         | 2 (3)              | <0.01 † |
| Vancomycin resistance (MIC >32 μg/ml) | 0 (0)                                                                                            | 0 (0)              | NA      |
| High-level gentamicin resistance      | 13 (19)                                                                                         | 31 (48)            | <0.01 † |
| Treatment and outcome                |                                                                                                |                    |         |
| 14-day mortality*                     | 11/69 (16)                                                                                       | 10/65 (15)         | 0.93    |

*Expressed as number of deaths/number of patients followed up (%). † Statistically significant, p ≤ 0.05. MIC: minimal inhibitory concentration, NA: not applicable.

TABLE 3. Clinical features of 70 patients with non-faecalis and non-faecium enterococcal bacteremia according to presence of the VanC phenotype

| Variable                              | Number (%) of patients with bacteremia caused by Enterococci without VanC phenotype (N=31) | VanC phenotype enterococci (N=39) | p value |
|---------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------|---------|
| Antibiotic resistance                 |                                                                                                |                                   |         |
| Vancomycin MIC*                       | 0.19-1.0 (0.5)                                                                                  | 2.0-8.0 (4)                       | ND      |
| Teicoplanin MIC*                      | 0.016-0.25 (0.125)                                                                             | 0.38-1.0 (0.5)                   | ND      |
| Ampicillin resistance                 | 11 (36)                                                                                         | 6 (15)                           | 0.05    |
| High-level gentamicin resistance      | 6 (19)                                                                                         | 7 (18)                           | 0.88    |
| Underlying disease or comorbid condition |                                                                                                |                                   |         |
| Cancer                                | 17 (55)                                                                                         | 20 (61)                          | 0.77    |
| Cancer with biliary obstruction       | 7 (23)                                                                                          | 7 (18)                           | 0.63    |
| Benign biliary disease                | 11 (36)                                                                                         | 12 (31)                          | 0.68    |
| Community-onset                       | 17 (55)                                                                                         | 15 (39)                          | 0.17    |
| Polymicrobial                         | 14 (45)                                                                                         | 19 (49)                          | 0.77    |
| APACHE II score †                     | 15±9                                                                                           | 14±7                             | 0.39    |
| Primary site of infection             |                                                                                                |                                   |         |
| Biliary tract                         | 15 (48)                                                                                         | 25 (64)                          | 0.19    |
| Urinary tract                         | 4 (13)                                                                                          | 1 (3)                            | 0.16    |
| Infective endocarditis                | 0 (0)                                                                                           | 1 (3)                            | >0.99   |
| Treatment and outcome                 |                                                                                                |                                   |         |
| Appropriate antibiotic treatment      | 18 (58)                                                                                         | 15 (39)                          | 0.10    |
| Persistent ‡ or recurrent bacteremia  | 0 (0)                                                                                           | 0 (0)                            | ND      |
| 14-day mortality‡                     | 3/31 (10)                                                                                       | 8/38 (21)                       | 0.20    |

*Expressed as range (median) μg/ml. † Expressed as mean (±SD). ‡ Persistent bacteremia was defined as the isolation of enterococci in blood cultures obtained from peripheral veins on ≥5 consecutive days despite appropriate antibiotic administration. §Expressed as number of deaths/number of patients followed up (%). APACHE: acute physiology and chronic health evaluation, MIC: minimal inhibitory concentration, ND: not done.

There was also no significant difference in outcome. Although five of the patients with bacteremia caused by VanC phenotype enterococci had undergone vancomycin therapy, no breakthrough or recurrent bacteremia was observed.

**DISCUSSION**

In this study, we showed that cases of non-faecalis and non-faecium enterococcal bacteremia were more likely to have biliary tract infection and polymicrobial bacteremia and were less likely to have infective endocarditis than were cases of *E. faecalis* bacteremia.

In the present study, biliary tract infection was significantly more common in non-faecalis and non-faecium enterococcal bacteremia than in *E. faecalis* bacteremia, in agreement with previous studies. The proportion of polymicrobial bacteremia (47%) in our study was similar to the
findings of previous studies: 44.6% to 50%.²,⁴,⁵

The anatomical site of infection should be taken into account in treating enterococcal infection, because the appropriate treatment strategy differs for different sites. In cases of endocarditis or meningitis, combination therapy with a cell-wall active agent plus an aminoglycoside should be used.¹,² However, in cases of enterococcal bacteremia without endocarditis or meningitis, there was no statistically significant difference in outcome between monotherapy and combination therapy in a number of studies.²³-²⁵

It has been described that infective endocarditis is significantly more common in *E. faecalis* bacteremia than in *E. faecium* bacteremia.²⁶ Previous reports showed that non-*faecalis* and non-*faecium* enterococci also have sufficient virulence to cause infective endocarditis on native heart valves in patients without predisposing valvular heart diseases.⁹-¹² However, the rate of infective endocarditis in non-*faecalis* and non-*faecium* enterococcal bacteremia had never been evaluated. In our study, we demonstrated for the first time that the rate of infective endocarditis in non-*faecalis* and non-*faecium* enterococcal bacteremia was only about 1%, and it was significantly lower than that in *E. faecalis* bacteremia. Our data suggest that routine echocardiography tests or aminoglycoside combination therapy is not necessary in patients with non-*faecalis* and non-*faecium* enterococcal bacteremia, unless the patient has suspicious signs of infective endocarditis such as persistent bacteremia, predisposing heart conditions, cardiac murmur, or metastatic infection.

Some workers have suggested that bacteremia due to VanC phenotype enterococci is associated with a low risk of mortality;² however, no comparative study was ever performed on the matter. In our comparative study, however, we found that the mortality in patients with bacteremia caused by VanC phenotype enterococci was not lower than that in patients with bacteremia caused by non-VanC non-*faecalis* and non-*faecium* enterococcal bacteremia. The outcome of non-*faecalis* and non-*faecium* enterococcal bacteremia did not affect mortality in patients with enterococcal bacteremia.

In conclusion, compared with patients with *E. faecalis* bacteremia, patients with non-*faecalis* and non-*faecium* enterococcal bacteremia were more likely to have biliary tract infection and polymicrobial bacteremia and were less likely to have infective endocarditis. The outcome of non-*faecalis* and non-*faecium* enterococcal bacteremia was not different from that of *E. faecalis* bacteremia. VanC phenotype did not affect mortality in patients with enterococcal bacteremia.

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**REFERENCES**

1. Murray BE. The life and times of the Enterococcus. Clin Microbiol Rev 1990;3:46-65.
2. Noskin GA, Peterson LR, Warren JR. Enterococcus faecium and Enterococcus faecalis bacteremia: acquisition and outcome. Clin Infect Dis 1995;20:298-301.
3. Choi SH, Lee SO, Kim TH, Chung JW, Choo EJ, Kwak YG, et al. Clinical features and outcomes of bacteremia caused by Enterococcus casseliflavus and Enterococcus gallinarum: analysis of 56 cases. Clin Infect Dis 2004;38:53-61.
4. de Perio MA, Yarnold PR, Warren J, Noskin GA. Risk factors and outcomes associated with non-Enterococcus faecalis, non-Enterococcus faecalis enterococcal bacteremia. Infect Control Hosp Epidemiol 2006;27:28-33.
5. Ratanasuwan W, Iwen PC, Hinrichs SH, Rupp ME. Bacteremia due to motile Enterococcus species: clinical features and outcomes. Clin Infect Dis 1999;28:1175-7.
6. Reid KC, Cockrell III FR, Patel R. Clinical and epidemiological features of Enterococcus casseliflavus/flavescens and Enterococcus gallinarum bacteremia: a report of 20 cases. Clin Infect Dis 2001;32:1540-6.
7. Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG Jr, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169:463-73.
8. Talarmin JP, Pineau S, Guillouzouic A, Bouttoule D, Giraudue C, Reynaud A, et al. Relapse of Enterococcus hirae prosthetic valve endocarditis. J Clin Microbiol 2011;49:1182-4.
9. Poyart C, Lambert T, Morand P, Abassade P, Quesne G, Baudouy Y, et al. Native valve endocarditis due to Enterococcus hirae. J Clin Microbiol 2002;40:2689-90.
10. Orito M, Gabrielli E, Caramma I, Rossotti R, Gambirasio M, Gervasoni C. Enterococcus gallinarum endocarditis in a diabetic patient. Diabetes Res Clin Pract 2008;81:e18-20.
11. Dargere S, Vermaud M, Verdon R, Saloux E, Le Page O, Leclercq R, et al. Enterococcus gallinarum endocarditis occurring on na-
tive heart valves. J Clin Microbiol 2002;40:2308-10.
12. Stepanović S, Jovanović M, Lavadinović L, Stosović B, Pelemis M. Enterococcus durans endocarditis in a patient with transposition of the great vessels. J Med Microbiol 2004;53:259-61.
13. Mirzoyev Z, Anavekar N, Wilson F, Uslan D, Baddour L, Mookadam F. Enterococcus avium endocarditis. Scand J Infect Dis 2004;36:876-8.
14. Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hooper DC, Johnson MP, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991;115:585-90.
15. Vergis EN, Hayden MK, Chow JW, Snyder DR, Zervos MJ, Linden PK, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia: a prospective multicenter study. Ann Intern Med 2001;135:484-92.
16. Devriese LA, Pot B, Kersters K, Lauwers S, Haesebrouck F. Acidification of methyl-alpha-D-glucopyranoside: a useful test to differentiate Enterococcus casseliflavus and Enterococcus gallinarum from Enterococcus faecium species group and from Enterococcus faecalis. J Clin Microbiol 1996;34:2607-8.
17. Facklam RR, Collins MD. Identification of Enterococcus species isolated from human infections by a conventional test scheme. J Clin Microbiol 1989;27:731-4.
18. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; eighteenth informational supplement. Wayne, PA: Clinical and Laboratory Standards Institute (CLSI), 2008;M100-S18.
19. Courvalin P. Vancomycin resistance in gram-positive cocci. Clin Infect Dis 2006;42(Suppl 1):S25-4.
20. Elliott TS, Foweraker J, Gould F, Perry JD, Sandoe JA; Working Party of the British Society for Antimicrobial Chemotherapy. Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2004;54:971-81.
21. Watanakunakorn C, Patel R. Comparison of patients with enterococcal bacteremia due to strains with and without high-level resistance to gentamicin. Clin Infect Dis 1993;17:74-8.
22. Graninger W, Ragette R. Nosocomial bacteremia due to Enterococcus faecalis without endocarditis. Clin Infect Dis 1992;15:49-57.
23. Gullberg RM, Homann SR, Phair JP. Enterococcal bacteremia: analysis of 75 episodes. Rev Infect Dis 1989;11:74-85.
24. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. Medicine (Baltimore) 1988;67:248-69.
25. Jang HC, Lee S, Song KH, Jeon JH, Park WB, Park SW, et al. Clinical features, risk factors and outcomes of bacteremia due to enterococci with high-level gentamicin resistance: comparison with bacteremia due to enterococci without high-level gentamicin resistance. J Korean Med Sci 2010;25:3-8.
26. Anderson DJ, Murdoch DR, Sexton DJ, Reller LB, Stout JE, Cabell CH, et al. Risk factors for infective endocarditis in patients with enterococcal bacteremia: a case-control study. Infection 2004;32:72-7.
27. Billot-Klein D, Gutmann L, Sablé S, Guittet E, van Heijenoort J. Modification of peptidoglycan precursors is a common feature of the low-level vancomycin-resistant VANB-type Enterococcus D366 and of the naturally glycopeptide-resistant species Lactobacillus casei, Pediococcus pentosaceus, Leuconostoc mesenteroides, and Enterococcus gallinarum. J Bacteriol 1994;176:2398-405.
28. Sahn DF, Free L, Handwerger S. Inducible and constitutive expression of vanC-1-encoded resistance to vancomycin in Enterococcus gallinarum. Antimicrob Agents Chemother 1995;39:1480-4.