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Original Article

# Clinical features and antimicrobial susceptibility of oral bacteria isolated from the blood cultures of patients with infective endocarditis

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## KEYWORDS

Antimicrobial prophylaxis;  
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**Abstract** *Background/purpose:* The epidemiology of infective endocarditis (IE) is under constant change due to the aging society and increases in antimicrobial-resistant pathogens. However, IE remains severe. This study aimed to review the current clinical characteristics of IE and the antimicrobial susceptibility of oral bacteria (OB) isolated from blood cultures to implement appropriate antimicrobial prophylaxis.

*Materials and methods:* We retrospectively investigated the clinical features of 180 patients with IE in whom OB and pathogens except OB (eOB) were identified as causative microorganisms via blood cultures. The susceptibility of the OB group to eight antibiotics was examined by broth microdilution.

*Results:* Among causative microorganisms, the isolation rate of staphylococci was slightly higher than that of OB; however, the difference was not significant (36.7% vs. 33.8%,  $p = 0.3203$ ). The number of patients with underlying cardiac disease was significantly higher in the OB group than in the eOB group (53.7% vs. 34.1%,  $p = 0.0113$ ). Only one ampicillin-resistant OB was detected (2.0%). OBs were significantly less susceptible to clarithromycin and azithromycin than to ampicillin (98.0% vs. 66.7% and 98.0% vs. 60.0%,  $p = 0.0003$  and  $p = 0.0003$ , respectively). Moreover, OBs were significantly less susceptible to clarithromycin and azithromycin than to clindamycin (66.7% vs. 88.2% and 60.0% vs. 88.2%,  $p = 0.0301$  and  $p = 0.0217$ , respectively). *Conclusion:* OBs were susceptible to ampicillin. However, the susceptibility of OBs to clarithromycin and azithromycin was significantly lower than that to ampicillin and clindamycin.

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These results are important and should help decisions regarding guide antimicrobial prophylaxis.

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## Introduction

Infective endocarditis (IE) is a life-threatening disease with various clinical symptoms, such as vascular embolization and heart failure due to the vegetation formed by the adherence of bacteria to damaged valves during transient bacteremia.<sup>1</sup> The diagnostic and treatment methods of IE have improved, although its associated mortality remains high.<sup>2</sup>

For many years, the correlation between dental procedures and IE onset has been indicated, and antimicrobial prophylaxis (AP) before dental procedures has been recommended for more than 50 years. However, several guidelines on AP before dental procedures have been revised. In the UK, although the implementation of AP was not recommended in any situation at all in 2008, this position was amended in 2016 to a recommendation that AP be considered in cases where patients are at a high risk for IE.<sup>3</sup> Other guidelines recommend AP before invasive dental procedures for patients at high risk of IE who have a medical history. The Japanese Cardiology Society (JCS) guidelines recommend the oral administration of amoxicillin 2 g or 30 mg/kg body weight as first-choice AP and clindamycin, azithromycin, or clarithromycin as second-line AP for patients with beta-lactam allergy before invasive dental procedures.<sup>4</sup> Other societies have made similar recommendations.<sup>5,6</sup> However, the reported increase in antimicrobial-resistant pathogens is a serious problem,<sup>7</sup> and changes in patient demographic characteristics and microbiological features have resulted in uncertainty regarding the need for and use of AP in the field of dentistry. There is little information on the antimicrobial susceptibility of oral bacteria in patients with actual IE.

Accordingly, this study aimed to understand the current circumstances surrounding IE to implement a precise prophylactic strategy for the use of antimicrobial agents. We retrospectively investigated the clinical features of patients with IE in whom oral bacteria (OB) were identified as causative microorganisms via blood cultures and assessed the microbiological features and oral susceptibility of the isolated OBs.

## Materials and methods

The protocol of this study was approved by the Declaration of Helsinki, and the ethics committee and institutional review board of Kobe City Medical Center General Hospital approved this study (approval number: zn210205). We applied the opt-out method on the hospital's website to obtain consent for participation in this study.

## Patient characteristics

For all patients included in this study, a definitive diagnosis of IE was established by a cardiologist, cardiovascular surgeon, and general internal physician based on the modified Duke's criteria.

Between October 1, 2011, and July 31, 2020, we retrospectively investigated the clinical features of 180 patients with IE treated at our hospital. Causative microorganisms assessed through blood cultures in all patients, and clinical data, such as age, sex, cardiac conditions regarded as risk factors for IE, and IE treatment and outcomes were compared between patients with IE caused by OB and those with IE caused by pathogens except oral bacteria (eOB). The presence or absence of dental procedures associated with IE was not evaluated because these were unclear in some cases.

Accordingly to The American Heart Association (AHA) Scientific Study, we defined viridans group streptococci (VGS; *Streptococcus anginosus*, *Streptococcus mutans*, *Streptococcus mitis*, *Streptococcus salivarius*, and *Streptococcus sanguinis*), nutritionally variant streptococci (NVS; *Abiotrophia defectiva* and *Granulicatella adiacens*), and *Cardiobacterium hominis* as OB.<sup>6</sup> We also defined culture-negative IE and causative microorganisms of IE that were not OB as eOB.

## Antimicrobial susceptibility

Antimicrobial susceptibility was analyzed in cases in which OB was isolated as the causative microorganism from blood culture. In patients with underlying cardiac disease, the incidence of OB with some form of antimicrobial resistance was compared with that in patients without underlying cardiac disease.

Biochemical identification was performed using the BD BACTEC FX Blood Culture System (Becton Dickinson, Sparks, MD, USA), and trypticase soy agar with 5% sheep blood/chocolate agar (Becton Dickinson, Sparks, MD, USA) was used for subculture. Antimicrobial susceptibility testing for ampicillin, penicillin G, ceftriaxone, clarithromycin, azithromycin, clindamycin, levofloxacin, and vancomycin was performed according to the agar dilution method of the Clinical Laboratory Standards Institute.<sup>8</sup>

## Statistical analysis

Statistical analysis was performed using Welch's t-test and Fisher's exact test for continuous and categorical variables, respectively. A *P*-value <0.05 was considered statistically significant.

## Results

### Causative microbiology

Blood culture results were positive in 160 (88.9%) patients. The causative microorganisms detected in this study are summarized in Fig. 1. The most frequently isolated pathogen was Staphylococci, which was detected in 59 (36.9%) patients, followed by OB, which was detected in 54 patients (33.8%) (48 VGS, 5 NVS, 4 alfa-streptococcus, and 1 *C. hominis*), enterococci, which was detected in 12 patients (7.5%), and other pathogens, which were detected in 35 patients (21.9%). There were no significant differences between OB and staphylococci ratios ( $p = 0.3200$ ).

### Patient characteristics

Patient demographic characteristics are summarized and compared between the OB and eOB groups in Table 1.

The mean patient age was  $67.6 \pm 17.9$  and  $64.7 \pm 18.6$  years in the eOB and OB groups, respectively, and the male/female ratio was 1.5. There were no significant differences in characteristics between both groups.

Valvular heart disease, including post-heart valve surgery, was the most common underlying cardiac disease in both groups. The number of patients with underlying cardiac disease in the OB group was significantly higher than that in the eOB group ( $p = 0.0113$ ). Regarding IE treatment, the surgery/conservative treatment ratio was not significantly different between groups, excluding one

patient in the eOB group who died the day after admission. Thirteen patients died in the eOB group; however, no patient in the OB group died ( $p = 0.0080$ ).

### Antimicrobial susceptibility

In 3/54 patients, we identified bacterial species, but antimicrobial susceptibility was unable to be determined due to poor growth. The antimicrobial susceptibility of clarithromycin and azithromycin was not tested in all cases due to changes in susceptibility panel; therefore, clarithromycin and azithromycin have been tested in 24 and 15 cases, respectively.

Clarithromycin and azithromycin showed significantly lower susceptibility rates than ampicillin (66.7% vs. 98.0% and 60.0% vs. 98.0%,  $p = 0.0003$  and  $p = 0.0003$ , respectively) (Table 2). Similarly, clarithromycin and azithromycin showed significantly lower susceptibility rates than clindamycin (66.7% vs. 88.2% and 66.0% vs. 88.2%,  $p = 0.0301$  and  $p = 0.0217$ , respectively) (Table 3).

There were no significant difference between the rate of VGS resistant to any drug isolated from patients at high risk of IE and those from patients without cardiac disease at high risk of IE (44.8% vs. 38.9%,  $p = 0.1601$ ).

## Discussion

Streptococci and staphylococci are the predominant causative microorganisms of IE.<sup>1,9,10</sup> Some reports in industrialized countries have described staphylococci as the most

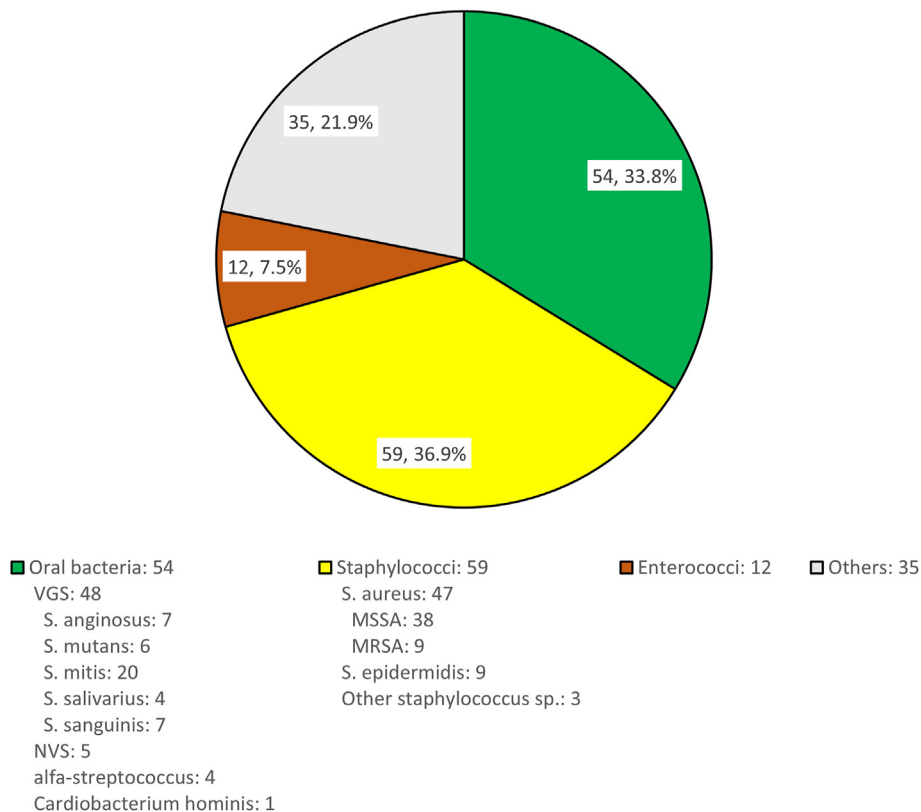


Figure 1 Causative microorganisms.

**Table 1** Clinical data of patients with infective endocarditis in the oral bacteria and excluding oral bacteria groups.

	eOB group (n = 126)	OB group (n = 54)	p-value
Age range (mean age), years	6–92 (67.6 ± 17.9)	20–93 (64.7 ± 18.6)	0.1653
Sex			0.5643
Male, n (%)	77 (61.1)	33 (61.1)	
Female, n (%)	49 (38.9)	21 (38.9)	
Cardiac condition, n (%)	43 (34.1)	29 (53.7)	0.0113
Valvular heart disease, including post-heart valve surgery	33	24	
Pacemaker implanted	10	4	
Ventricular septal defect	2	3	
Previous episode of IE	2	0	
Hypertrophic cardiomyopathy	0	1	
Bicuspid aortic valve	1	0	
Treatment of IE			
Surgical treatment, n (%)	51 (40.8)	29 (51.9)	0.0765
Mortality, n (%)	13 (10.3)	0 (0)	0.0080

eOB, excluding oral bacteria; OB, oral bacteria; and IE, infective endocarditis.

common causative microorganism of IE. In this study, the reason behind the fact that no significant differences were observed between the OB and staphylococci ratios might be because our hospital is an acute facility where hospitalization periods are relatively short; moreover, staphylococcal IE is a commonly healthcare-associated disease, and its severity is correlated with hospitalization duration.<sup>11</sup>

**Table 2** Antimicrobial susceptibility data.

	Susceptibility, % (n)	p-value*
Ampicillin	98.0 (50/51)	
Penicillin	98.0 (50/51)	
Ceftriaxone	100 (51/51)	
Clarithromycin	66.7 (16/24)	0.0003
Azithromycin	60.0 (9/15)	0.0003
Clindamycin	88.2 (45/51)	0.0560
Levofloxacin	92.2 (46/51)	0.1023
Vancomycin	100 (51/51)	

\*Differences between the antimicrobial susceptibility of clarithromycin, azithromycin, clindamycin, and levofloxacin and that of ampicillin were deemed significant at a p-value of <0.05.

**Table 3** Antimicrobial susceptibility to clarithromycin and azithromycin compared with that of clindamycin.

	Susceptibility, % (n)	p-value*
Clindamycin	88.2 (45/51)	
Clarithromycin	66.7 (16/24)	0.0253
Azithromycin	60.0 (9/15)	0.0127

\*Differences were deemed significant at a p-value of <0.05.

Patient age was widely distributed. Over 70% of patients were aged over 60 years, and over 50% of patients were aged over 70 years in both groups. IE commonly affects both old and male patients. Studies in other industrialized nations had age and sex ratios similar to those of this study.<sup>9</sup> There was a notably high number of patients with IE with pacemaker implantation, although AP was not recommended in the AHA<sup>6</sup> and ESC<sup>5</sup> guidelines. According to JCS, patients with pacemaker implantation are at moderate risk for IE; however, the incidence of pacemaker implantation-associated IE tended to increase in recent years.<sup>1</sup> AP before invasive dental procedures for patients with pacemakers should be carefully considered.

The number of patients with underlying cardiac conditions in the OB group was significantly higher than that in the eOB group, suggesting the importance of validating and confirming AP before such patients undergo invasive dental procedures. The mortality rate in the eOB group was significantly higher than that in the OB group, indicating that the clinical course of staphylococcal IE is acute and is likely to become severe whereas that of streptococcal IE is subacute.<sup>1,5</sup> The mortality rates of enterococcal and streptococcal IE were not significantly different.<sup>12</sup>

In this study, all OBs were susceptible to ampicillin, penicillin G, and ceftriaxone, except for one isolate, *S. sanguinis*, which was resistant to ampicillin. Some Japanese authors reported that the rate of amoxicillin resistance in VGS was extremely low, which was similar to the results of this study; approximately 5% of the ampicillin- and amoxicillin-resistant VGSs described in Japan are resistant.<sup>9,13–15</sup> In Western countries, approximately 15% of VGSs are reportedly amoxicillin-resistant; moreover, the incidence of amoxicillin-resistant VGS has increased.<sup>16–18</sup> Although susceptibility to amoxicillin varies between regions, and the number of resistant VGSs has also increased over the years, yet the incidence of ampicillin- and amoxicillin-resistant VGSs may be low in Japan today. Moreover, amoxicillin is indicated as the most appropriate for AP considering current recommendations and its convenience.

The incidence rate of penicillin-resistant VGSs isolated from patients at high risk for IE was higher than that from healthy Japanese people because patients at risk of IE are frequently prescribed antimicrobial agents before invasive procedures according to the recommended AP guidelines.<sup>19</sup> In fact, amoxicillin is the most commonly prescribed antimicrobial agent for IE prophylaxis.<sup>14,20</sup> In many countries, including Japan, amoxicillin also tends to be frequently prescribed for odontogenic infection.<sup>17,21–24</sup> Accordingly, the incidence of amoxicillin-resistant VGSs may continue to increase. In this study, there were no significant differences

in the rate of any antimicrobial-resistant VGSs isolated from patients at either high or low risk for developing IE.

Several guidelines recommend clindamycin, clarithromycin, and azithromycin as second-choice prophylactic antimicrobial agents.<sup>5,6</sup> These drugs have been also widely used to treat odontogenic infections in patients with allergies to beta-lactams.<sup>25–27</sup> However, this study showed that the susceptibility of OBs to clarithromycin and azithromycin was low. Although there were no significant differences in susceptibility to ampicillin and clindamycin, 10% of OBs were resistant to clindamycin in this study. Similar to other antimicrobial agents, some authors have reported that clindamycin-resistant pathogens have recently increased.<sup>13,27–29</sup> The choice of antimicrobial agent of prophylaxis for patients at high risk for IE with beta-lactam allergy was carefully considered. In contrast, no OB in this study was resistant to ceftriaxone, a third-generation cephalosporin which is a beta-lactam antimicrobial agent that is similar to penicillin. VGSs are generally susceptible to ceftriaxone, a third-generation cephalosporin.<sup>13,22,30</sup> Cross-reactivity between penicillins and second- and third-generation cephalosporins is negligible;<sup>27,31</sup> therefore, the intravenous administration of ceftriaxone may be considered for patients at a high risk of IE with an allergy to penicillin able to take oral medication.

IEs are rarely caused by the NVS and HACEK (*Haemophilus aphrophilus*, *Haemophilus paraprophilus*, *Aggregatibacter actinomycetemcomitans*, *C. hominis*, *Eikenella corrodens*, and *Kingella kingae*, which are normal flora in the oral cavity) group organisms, with an incidence of 4%–8% and 1%,<sup>1,32</sup> respectively. NVS members are less susceptible to penicillin, ceftriaxone, and erythromycin. Moreover, the rates of susceptibility to penicillin and ceftriaxone show species-related differences.<sup>32,33</sup> Some HACEK organisms have been reported to produce beta-lactamases. Therefore, ampicillin is not considered the first-line treatment option.<sup>5</sup> Third- or fourth-generation cephalosporins, such as ceftriaxone, have commonly been used to treat HACEK IE.<sup>34</sup> However, there is no consensus on whether it targets NVS or HACEK organisms. In this study, 5 NVS and *C. hominis* organisms were susceptible to all 8 antimicrobial agents, except for *Abiotrophia defectiva*, which was resistant to clindamycin. A prophylactic regimen that targets NVS and HACEK should be released.

Nakano et al. reported that more than 90% of dentists recognize the importance of prophylaxis for IE.<sup>35</sup> However, the JCS guidelines recommend the administration of amoxicillin 2 g or 30 mg/kg before an invasive procedure in adults, whereas the Japanese Society of Chemotherapy recommends 500 mg of amoxicillin. These differing recommendations could confuse practitioners and obstruct proper implementation; moreover, the overuse and misuse of antimicrobial agents may increase the number of antimicrobial-resistant pathogens.

This study has some limitations. A single-center study with a small sample size does not have the power to detect statistically significant differences. Microbiological features differ among facilities, regions, and time periods. Our hospital is an acute facility, meaning that bias may have occurred among facilities. The susceptibility test panel used at our hospital changed during the study period, reducing the sample size of pathogens that were tested for

susceptibility to clarithromycin and azithromycin. This study demonstrated high rates of susceptibility of OB to ampicillin and ceftriaxone, and these antimicrobial agents were suitable as the first choice for AP, whereas clarithromycin and azithromycin might no longer be considered second-line AP. Regarding patient characteristics, AP might be more necessary before invasive dental procedures in patients with underlying heart disease since the number of patients with underlying cardiac disease was significantly higher in the OB group than in the eOB group. We expect that this study will help practitioners implement AP; global surveillance studies are warranted to provide verified evidence that could enable the implementation of definite recommendations.

## Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

## Acknowledgements

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