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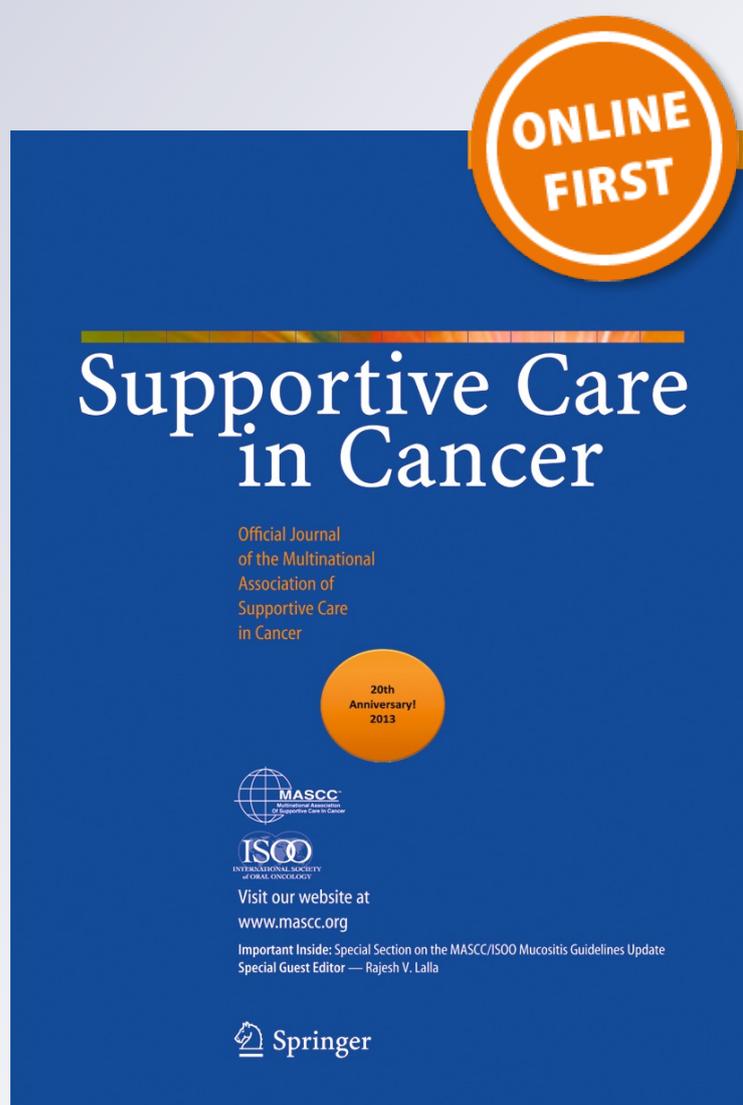
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# Periodontal status and bacteremia with oral viridans streptococci and coagulase negative staphylococci in allogeneic hematopoietic stem cell transplantation recipients: a prospective observational study

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## Abstract

**Aim** This study was aimed to investigate whether any association could be found between the presence of an inflamed and infected periodontium (e.g., gingivitis and periodontitis) and the development of bacteremia during neutropenia following allogeneic hematopoietic stem cell transplantation (HSCT).  
**Methods** Eighteen patients underwent a periodontal examination before HSCT. Patients were classified as periodontally

healthy [all periodontal pocket depths (PPD) ≤ 4 mm and bleeding on probing (BOP) ≤ 10 %] or as having gingivitis/periodontitis [PPD ≥ 4 mm and BOP > 10 %]. Oral mucositis (OM) was scored using the daily mucositis score. Blood cultures were taken at least twice weekly.  
**Results** Five patients were periodontally healthy, while 13 patients had gingivitis or periodontitis. Twelve patients (67 %) developed bacteremia during neutropenia, of which

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11 patients (61 %) had one or more episodes of bacteremia due to coagulase-negative staphylococci (CONS, most often *Staphylococcus epidermidis*) or to oral viridans streptococci (OVS), or both. Patients with gingivitis/periodontitis more often had bacteremia than those with a healthy periodontium ( $p=0.047$ ), and BOP was associated with bacteremia ( $p=0.049$ ). All patients developed ulcerative OM, but its severity and duration were not associated with bacteremia. OM duration and the length of stay in the hospital were strongly correlated ( $R=0.835$ ,  $p\leq 0.001$ ).

**Conclusion** This study indicates that periodontal infections may contribute to the risk of developing OVS and CONS bacteremia during neutropenia following HSCT. While our results point to the importance of periodontal evaluation and management before HSCT, further studies on periodontal contribution to systemic infectious complications are warranted.

**Keywords** Periodontal disease · Gingivitis · Bacteremia · Hematopoietic stem cell transplantation · Coagulase negative staphylococci · Viridans streptococci

## Introduction

Periodontal infections are inflammatory diseases caused by a bacterial biofilm (dental plaque) that affect the tissues surrounding the teeth. In gingivitis, the infection is limited to the gingiva, and the condition is reversible by practicing good oral hygiene. In periodontitis, the inflammation extends deep into the tissues affecting the attachment apparatus of the tooth. Gingivitis and moderate periodontitis are common, and its prevalence increases with age. The prevalence of gingivitis is estimated to be 50 % [1], whereas the prevalence of severe forms of periodontitis is estimated to be 10–15 % in Western nations [2]. However, in patients suffering from hematologic malignancies, the prevalence of gingivitis and periodontitis may be higher [3, 4].

Inflammation of periodontal tissues results in deepening of the gingival crevice and formation of periodontal pockets, which act as a reservoir for a wide variety of microorganisms. Periodontal infections may not only affect the oral tissues, but bacteria may translocate into the blood stream via ulcerated inflamed crevice and pocket epithelium and the adjacent gingival microcirculation. This may occur following invasive dental procedures and also during normal daily activities such as chewing and tooth brushing [5–10]. Bacteremia and low-grade systemic inflammation induced by periodontal infections may confer a risk for systemic conditions including infective endocarditis and other cardiovascular diseases, stroke, premature low birth weight delivery, and diabetes mellitus [11].

An inflammatory and infectious periodontal condition increases morbidity and may have deleterious effects in neutropenic patients with cancer [12–14]. There is evidence from experimental studies that bacteria invade periodontal tissues in the absence of polymorphonuclear neutrophils [15], and cancer chemotherapy may increase ulceration of pocket epithelium. Bacteremia and sepsis due to Gram-negative facultative or strictly anaerobic bacteria typically associated with periodontal diseases have been reported [16–20], but are relatively rare. In contrast, bacteremia associated with oral *Streptococcus* species and *Staphylococcus* species develops frequently in these patients [21]. It is well known that the oral cavity is the most likely origin of bacteremia due to viridans streptococci (OVS) such as *Streptococcus mitis* and *Streptococcus oralis*, particularly in the setting of ulcerative oral mucositis (OM) [21, 22]. Bacteremia caused by coagulase-negative staphylococci (CONS) often originates from the skin, although these bacteria may be also present at oral mucosal surfaces [23, 24], in saliva [25], and in periodontal pockets [26–28]. The proportional recovery of supragingival *Staphylococcus* spp. was found to increase in patients with periodontitis during treatment with myelosuppressive chemotherapy [29]. Peterson et al. [30] found *Staphylococcus epidermidis*, *Candida albicans*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* to be the predominant subgingival microorganisms associated with acute exacerbations of chronic periodontal disease in myelosuppressed cancer patients. Kennedy et al. [31] described *S. epidermidis* and *Streptococcus oralis* bacteremia in a hematopoietic stem cell transplantation (HSCT) recipient, originating from the oral cavity as determined by molecular characterization.

Periodontal infections potentially contribute to bacteremia in patients rendered neutropenic after treatment with high-dose chemotherapy to prepare them for an allogeneic HSCT, and the role played by these infections may be underestimated [32]. The present study is set out to determine whether there is any association between the presence of an inflamed and infected periodontium (e.g., gingivitis and periodontitis) and the development of bacteremia during the neutropenic phase of allogeneic HSCT.

## Patients and methods

During 2000 and the first half of 2001, 18 adult patients that were to receive a myeloablative allogeneic HSCT at the University Medical Centre, St. Radboud Nijmegen participated in this prospective, observational study. The study was approved by the Committee for Scientific Studies in Humans, and written informed consent was obtained from all patients. An oral, dental, and periodontal examination was performed by one trained examiner (GG) at the

College of Dental Sciences of the Radboud University Nijmegen Medical Centre prior to admission to the hospital. Periodontal measurements included the plaque index (PI, which is a measure for oral hygiene) [33], probing pocket depth (PPD), and the percentages of sites with bleeding on probing (BOP, a measure for gingival inflammation). These measurements were recorded at four sites per tooth (mesio-buccal, mesiolingual, distobuccal, and distolingual). Probing depths measurements were rounded off to the nearest millimeter. The dentition and oral mucosal surfaces were inspected for pathology, and panoramic radiographs were taken. Patients were divided into two groups: periodontally healthy (defined as a  $PPD \leq 4$  mm and  $BOP \leq 10$  % for all teeth), and a gingivitis ( $PPD \leq 4$  mm,  $BOP > 10$  %) plus periodontitis group ( $PPD > 4$  mm and  $BOP \geq 10$  %).

On admission, a double lumen central venous catheter was inserted that was used for delivering medication and obtaining blood samples. Patients received ciprofloxacin for selective antibacterial prophylaxis, valaciclovir for antiviral prophylaxis, and co-trimoxazole to prevent *Pneumocystis pneumonia*. During their hospital stay, patients were given oral care aimed at preventing the accumulation of dental plaque and keeping the oral tissues moist. No antimicrobial mouth rinses were used. Mucositis was scored by the nursing staff using the daily mucositis score (DMS), a score that was specifically developed to investigate the connection between OM with fever and bacteremia [34]. Mucositis was regarded as mild (DMS score 1–4), moderate DMS score (DMS 5–9), or severe ( $DMS \geq 10$ ).

During neutropenia (absolute neutrophil count of  $\leq 500/\mu\text{l}$  blood), blood cultures were taken twice weekly for surveillance and more often to investigate fever. For surveillance, 10 ml blood was drawn from each lumen of the catheter and incubated aerobically at 37 °C. To investigate fever, 10 ml blood was drawn from each lumen of the catheter as for surveillance blood cultures, and a further 40 ml blood was drawn from a peripheral vein and inoculated into two sets of aerobic and anaerobic Bactec bottles. The blood cultures were examined for growth for 5 days. When growth was detected, the sample was removed, inoculated onto blood agar plates, and incubated aerobically and anaerobically for 24–48 h to isolate the responsible bacterium. All isolates were identified and tested for antibiotic susceptibility. Bacteremia was defined by recovery from at least one blood culture of any bacterium with the exception of skin commensals such as *S. epidermidis* or other CONS for which recovery of the same species from at least two blood cultures was required.

## Statistics

Associations between nominal variables were calculated using the Fisher's exact test in the case of a  $2 \times 2$  table.

Differences in means between groups were calculated with the nonparametric Mann–Whitney *U* test. Correlations between the PI, BOP scores, and mucositis scores were calculated with the Pearson's correlation coefficient. A  $p < 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS version 18.0.

## Results

Patient characteristics and conditioning regimens are summarized in Table 1. Five patients (28 %) were considered to be periodontally healthy, while 13 patients had gingivitis or periodontitis (Table 2). The mean PI was 1.36 ( $SD \pm 0.58$ ), whereas mean BOP was 17.6 % ( $SD \pm 11.8$ ).

None of the patients had extensive dental caries or any oral mucosal inflammatory or infectious condition including pericoronitis before HSCT. In addition, the panoramic X-rays revealed no profound dental caries threatening the pulp in any of the patients. One patient (number 12, Table 2) in the gingivitis/periodontitis group also had a potential periapical infectious focus around two resected apices that may have contributed to bacteremia with *S. epidermidis*. Following conditioning, all patients developed ulcerative OM and neutropenia. All patients developed moderate or severe mucositis with a mean peak DMS of 9.0 (range, 5–14). The mean duration of OM (any grades) was 27 days with a range of 11–53 days.

**Table 1** Patient characteristics and conditioning regimen

Number of patients	18
Male	11 (61 %)
Female	7 (39 %)
Age (mean $\pm$ SD and range in years)	41.8 ( $\pm 13.4$ ; 19–64)
Diagnosis	
Chronic myeloid leukemia	5 (28 %)
Acute lymphoblastic leukemia	4 (22 %)
Acute myeloid leukemia	3 (17 %)
Multiple myeloma	3 (17 %)
Non-Hodgkin lymphoma	1 (6 %)
Myelodysplastic syndrome	1 (6 %)
Chronic lymphocytic leukemia	1 (6 %)
Conditioning regimen	
Cy + IDA + Bu	2 (13 %)
Cy + TBI (9 Gy unfractionated)	5 (28 %)
Cy + TBI (9 Gy unfractionated) + ATG	5 (28 %)
Cy + IDA + TBI (9 Gy unfractionated)	6 (33 %)

Cy cyclophosphamide, IDA idarubicin, Bu busulfan, TBI total body irradiation, Gy Gray, ATG antithymocyte globulin

**Table 2** Periodontal status and bacteremia

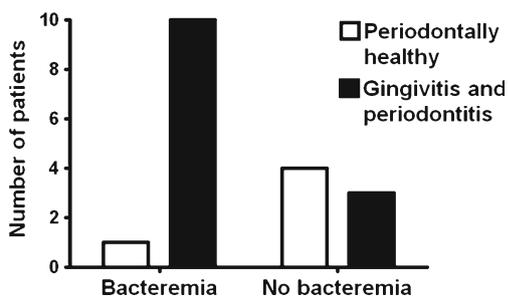
Patient number	Number of pockets with PPD $\geq$ 4 mm	BOP (%)	Periodontal condition	Episodes of OVS and/or CONS bacteremia	Isolated microorganisms
1	5 (=4 mm)	4	Healthy	None	NA
2	1 (=4 mm)	2	Healthy	None	<i>Escherichia coli</i>
3	None	5	Healthy	2	<i>Staphylococcus epidermidis</i> and <i>Micrococcus</i> species
4	4 (=4 mm)	5	Healthy	None	NA
5	1 (=4 mm)	5	Healthy	None	NA
6	1 (>4 mm)	13	Gingivitis/periodontitis	None	NA
7	None	12	Gingivitis	7	<i>Staphylococcus epidermidis</i>
8	None	31	Gingivitis	2	<i>Staphylococcus epidermidis</i>
9	2 ( $\geq$ 4 mm)	18	Gingivitis/periodontitis	None	NA
10	3 ( $\geq$ 4 mm)	14	Gingivitis/periodontitis	2	<i>Streptococcus mitis</i>
11	4 ( $\geq$ 4 mm)	14	Gingivitis/periodontitis	1	<i>Staphylococcus epidermidis</i>
12 <sup>a</sup>	4 ( $\geq$ 4 mm)	22	Gingivitis/periodontitis	2	<i>Staphylococcus epidermidis</i>
13	7 ( $\geq$ 4 mm)	24	Gingivitis/periodontitis	2	<i>Streptococcus oralis</i> and <i>Staphylococcus epidermidis</i>
14	11 ( $\geq$ 4 mm)	42	Gingivitis/periodontitis	3	<i>Staphylococcus epidermidis</i>
15	14 ( $\geq$ 4 mm)	26	Gingivitis/periodontitis	1	<i>Streptococcus mitis</i> and <i>Staphylococcus epidermidis</i>
16	20 ( $\geq$ 4 mm)	30	Gingivitis/periodontitis	None	NA
17	31 ( $\geq$ 4 mm)	19	Gingivitis/periodontitis	2	<i>Streptococcus acidominimus</i> and <i>Staphylococcus epidermidis</i>
18	32 ( $\geq$ 4 mm)	40	Gingivitis/periodontitis	4	<i>Staphylococcus epidermidis</i> and <i>Streptococcus mitis</i>

BOP bleeding on probing, CONS coagulase negative staphylococci, OVS oral viridans streptococci, PPD periodontal probing depth

<sup>a</sup>This patient also had a potential periapical infectious focus

Twelve patients (67 %) developed bacteremia, of which 11 patients had one or more episodes with bacteremia with CONS or OVS or both (Table 2). Bacteremia was most often due to *S. epidermidis* and OVS bacteremia due to *S. mitis*, *S. oralis*, and *Streptococcus acidominimus*. Four patients developed bacteremia due to both CONS and OVS. *Escherichia coli* bacteremia affected one patient. No anaerobes were detected in any of the blood cultures.

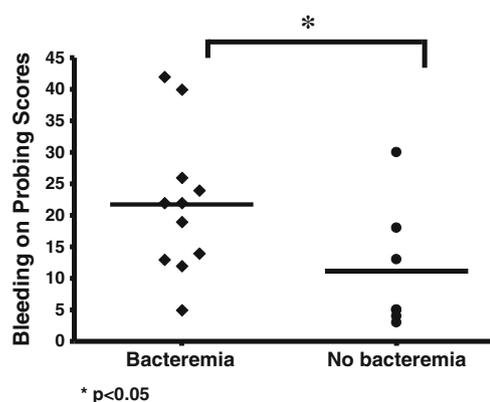
Patients with gingivitis/periodontitis more often developed bacteremia during neutropenia than did those with a healthy periodontium ( $p=0.047$ ) (Fig. 1), and



**Fig. 1** Distribution of bacteremia and periodontal status

BOP scores were found to be significantly higher in those with bacteremia ( $p=0.049$ ) (Fig. 2). Patients who developed bacteremia had an average BOP score of  $21.7\pm 11.3$ , compared with an average BOP score of  $11.1\pm 10.0$  for those who did not.

No significant differences were found between patients who did and those who did not develop



**Fig. 2** Bleeding on Probing Scores and the presence of bacteremia

bacteremia with regard to the number of pockets with  $\text{PPD} \geq 4$  mm, the amount of dental plaque (PI) present before HSCT, peak OM scores, the duration of OM (any grades, as well as ulcerative mucositis), prevalence and duration of fever, and length of stay in the hospital (LOS). In addition, PI scores as well as the periodontal condition, including BOP, were not significantly associated with peak OM scores, OM duration, number of febrile days, and LOS. There was a significant correlation between the duration of OM and LOS ( $R=0.835$ ,  $p<0.001$ , Fig. 3).

## Discussion

The findings of this study suggest that gingivitis and periodontitis, particularly gingival inflammation assessed by BOP, may represent a risk factor for bacteremia due to OVS and CONS during the neutropenic phase of HSCT.

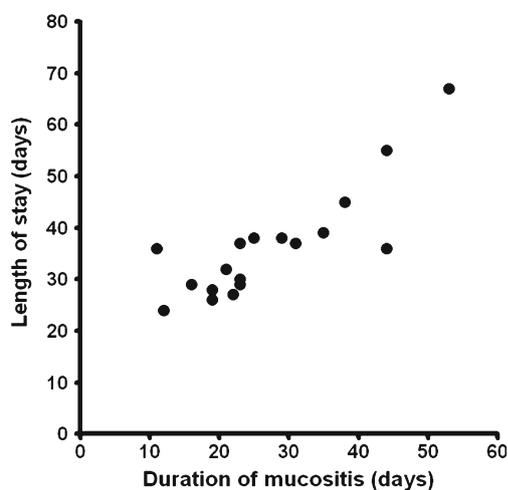
There is evidence from a large number of studies in patients without cancer that inflamed and ulcerated crevicular or pocket epithelium around the teeth may act as a portal of entry for bacteria into the blood stream. Lockhart et al. [7] showed that the generalized presence of gingival bleeding after tooth brushing (which is a sign of inflammation due to gingivitis or periodontitis) was associated with an almost eightfold increase in bacteremia risk, whereas no associations could be found with other measures of periodontal disease, including PPD. This is consistent with another study reporting the incidence and the magnitude of bacteremia induced by chewing, tooth brushing, and invasive dental procedures to be associated with gingival inflammation rather than with pocket depths [5]. Bacteremia originating

from the oral cavity can be associated with a wide variety of microorganisms, including Gram-negative anaerobe bacteria, OVS, and CONS. For instance, it is estimated that approximately 50 % of all cases of infective endocarditis are caused by oral OVS [35, 36]. Oral mucosal tissues as well as the periodontium may harbor CONS [23, 27], and streptococci may be replaced by CONS following HSCT, particularly in patients on long-term antibiotics [24]. *S. oralis* and *S. epidermidis* originating from the oral cavity were shown to cause an episode of bacteremia in a neutropenic HSCT patient using DNA identification methods [31].

While we can only speculate on the route of hematologic dissemination, it is reasonable to consider that bacteria may enter the circulation via inflamed and ulcerated periodontal tissues. Experimental studies indicate that cancer chemotherapy exaggerates ulceration of periodontal pocket epithelium by direct toxicity and by myelosuppression [37] and increases periodontal capillary density [38], thereby further increasing bacteremia risk. Periodontal pockets might also act as a reservoir for bacteria that translocate into the oral cavity and then enter the circulation via the damaged mucosal membranes associated with OM. Hyposalivation and other impaired oral defense mechanisms may contribute to this risk. Furthermore, it is possible that bacteria find their way from the periodontium into the blood stream via mucosal barrier damage of the epithelial lining of the lungs or the gastrointestinal tract. Once in the blood stream of a neutropenic and otherwise immunocompromised host, bacteria may colonize distant organs and central venous lines.

Periodontitis has also been associated with neutropenic fever in a patient with leukemia without the presence of bacteria in the blood stream [39]. Bergmann [40] identified oral infections including gingivitis and periodontitis as an important cause of fever in patients with hematological malignancies. Laine et al. [41] reported more episodes of fever in lymphoma patients with a poor oral condition, particularly periodontitis. A recent study indicated that intensive oral care performed by dental professionals before and during HSCT reduced the incidence of febrile neutropenia and OM [42]. Our findings suggest that gingivitis and periodontitis may be a risk factor for neutropenic fever, although we did not find any differences between patients with a healthy periodontium and those with gingivitis/periodontitis with respect to the prevalence or the duration of fever. However, the number of patients in our study was small, and it should be noted that all patients developed ulcerative OM that is considered to be an important risk factor for neutropenic fever [43]. We did not identify an association between periodontal health, the plaque index prior to HSCT, and OM severity and duration.

Other oral pathologies, including an infected and inflamed pulp, also represent a potential origin of OVS and



**Fig. 3** Relationship between duration of oral mucositis and length of stay

CONS bacteremia [44]. In our study, only one patient in the gingivitis/periodontitis group also had a potential periapical infectious focus.

Our findings suggest that the oral cavity may be the origin of CONS bacteremia. A retrospective study found no association between radiographic periodontal bone loss and risk for septicemia in HSCT recipients [45]. Bacteremia with *S. epidermidis* developed most frequently, but this microorganism was not considered to likely originate from the oral cavity. Larger prospective studies using PPD and BOP measurements should be performed and a recently developed index quantifying the periodontal inflamed surface area may prove useful [46]. In addition, molecular DNA fingerprinting techniques are needed to assess the relative contribution of gingivitis and periodontitis to systemic infectious complications. Such longitudinally designed studies should evaluate the prevalence of OVS and CONS as well as other microorganisms in sub- and supragingival dental plaque and oral mucosal surfaces and compare DNA profiles with those of microorganisms isolated from the blood stream and with those recovered from intravenous lines or other potential sites of infection.

In the past, studies focused primarily on acute periodontal infections that may develop during neutropenia [30]. However, nowadays, these exacerbations of pre-existent chronic gingivitis and periodontitis are relatively uncommon. This decrease may be associated with changes in prophylactic antibiotic and antiviral regimens over the last decades. In contrast, chronic asymptomatic periodontal infections are common, and our preliminary results indicate that these infections may be associated with systemic infection. Nevertheless, periodontal infections can be easily overlooked or misdiagnosed, particularly when symptoms of gingival inflammation are masked by neutropenia. Diagnosis requires an oral evaluation including a thorough periodontal examination performed prior to the neutropenic phase. At the time of this study (2000–2001), such an evaluation was not routinely performed at our center, and oral infections including gingivitis/periodontitis were not managed systematically prior to HSCT. Nowadays, patients are referred to a dental professional using a detailed checklist as part of their HSCT workup. More studies are needed on the relative contribution of periodontal infections to local and systemic complications in HSCT patients as well as on the efficacy of protocols for management of these infections. The results of this study point to the importance of an oral evaluation before HSCT as well as interventions before and during HSCT to reduce the microbiological load (e.g., by periodontal treatment and meticulous oral hygiene measures) and thereby reducing gingival inflammation. This may significantly reduce the overall risk for complications [42, 47], including OVS and CONS bacteremia.

**Disclosures** No disclosures with a potential conflict of interest with the present observational study.

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