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Antibiotic prophylaxis with amoxicillin to prevent infective endocarditis in periodontitis patients reconsidered: a narrative review

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Abstract: **OBJECTIVES** To discuss first, the adequacy of the antibiotic prophylaxis regimen currently recommended for the prevention of infective endocarditis in periodontitis patients, and second, preventive measures to decrease the rate of bacteraemia after periodontal treatment. **MATERIALS AND METHODS** A bibliographic literature search identifying clinical trials between January 1990 and January 2021, focusing on microorganisms in bacteraemia after periodontal treatment and bacteria in infective endocarditis, was performed. Two reviewers independently identified and screened the literature by systematically searching in Medline/Premedline, EMBASE and Cochrane Library. **RESULTS** Two hundred and seventy articles were identified, of which twenty-three met the inclusion criteria. Bacteraemia rates after periodontal treatment ranged from 10-94% in the investigated patients. Mainly oral pathogens related to infective endocarditis, such as viridans group streptococci (up to 70%) and HACEK group pathogens (e.g., *Aggregatibacter actinomycetemcomitans*), were detected. But typical oral and periodontopathogenic species, such as *Porphyromonas* spp. (*P.s gingivalis*) (up to 50%), *Actinomyces* spp. (up to 30%) and *Fusobacterium* spp. (up to 30%), which do not usually cause infective endocarditis, were also found. Infective endocarditis episodes that might have been in association with a dental treatment were mainly caused by viridans group streptococci. Prophylactic measures like rinse application of chlorhexidine, povidone-iodine or essential oils, diode laser or systemic antibiotic prescription were described as decreasing the bacteraemia rate after periodontal interventions to 5-70%. **CONCLUSION** The currently recommended systemic antibiotic prophylaxis with amoxicillin before periodontal treatment in high-risk cardiovascular patients still covers the most common oral bacteria causing infective endocarditis, namely viridans group streptococci, and therefore seems adequate in this context. Since bacteraemia, not infective endocarditis, is the endpoint in most studies, the causality between bacteraemia after periodontal treatments and infective endocarditis remains difficult to elucidate. Until more evidence is available regarding this, adherence to current guidelines for antibiotic prophylaxis in patients at high risk for infective endocarditis undergoing periodontal treatment remains recommended.

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Antibiotic prophylaxis with amoxicillin to prevent infective endocarditis in periodontitis patients reconsidered: a narrative review

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Summary

OBJECTIVES: To discuss first, the adequacy of the antibiotic prophylaxis regimen currently recommended for the prevention of infective endocarditis in periodontitis patients, and second, preventive measures to decrease the rate of bacteraemia after periodontal treatment.

MATERIALS AND METHODS: A bibliographic literature search identifying clinical trials between January 1990 and January 2021, focusing on microorganisms in bacteraemia after periodontal treatment and bacteria in infective endocarditis, was performed. Two reviewers independently identified and screened the literature by systematically searching in Medline/Premedline, EMBASE and Cochrane Library.

RESULTS: Two hundred and seventy articles were identified, of which twenty-three met the inclusion criteria. Bacteraemia rates after periodontal treatment ranged from 10–94% in the investigated patients. Mainly oral pathogens related to infective endocarditis, such as viridans group streptococci (up to 70%) and HACEK group pathogens (e.g., *Aggregatibacter actinomycetemcomitans*), were detected. But typical oral and periodontopathogenic species, such as *Porphyromonas* spp. (*P.s gingivalis*) (up to 50%), *Actinomyces* spp. (up to 30%) and *Fusobacterium* spp. (up to 30%), which do not usually cause infective endocarditis, were also found. Infective endocarditis episodes that might have been in association with a dental treatment were mainly caused by viridans group streptococci. Prophylactic measures like rinse application of chlorhexidine, povidone-iodine or essential oils, diode laser or systemic antibiotic prescription were described as decreasing the bacteraemia rate after periodontal interventions to 5–70%.

CONCLUSION: The currently recommended systemic antibiotic prophylaxis with amoxicillin before periodontal treatment in high-risk cardiovascular patients still covers the most common oral bacteria causing infective endocarditis, namely viridans group streptococci, and therefore

seems adequate in this context. Since bacteraemia, not infective endocarditis, is the endpoint in most studies, the causality between bacteraemia after periodontal treatments and infective endocarditis remains difficult to elucidate. Until more evidence is available regarding this, adherence to current guidelines for antibiotic prophylaxis in patients at high risk for infective endocarditis undergoing periodontal treatment remains recommended.

Introduction

Periodontitis is found in about 36–45% of the population, whereas gingivitis is nearly ubiquitous, in up to 90% [1, 2]. In a healthy oral cavity, a multitude of bacteria are present, with a significantly higher number and variety of microorganisms in patients suffering from periodontitis [3–5]. Periodontal breakdown is driven by the dominance of several pathogens of the oral cavity at different time points of the disease's development. Socransky and his co-workers described, back in 1998, the typical bacterial complexes involved in periodontal destruction [6, 7]: the orange complex includes pathogens which are important to the initiation of periodontal disease, such as *Prevotella intermedia*, *Fusobacterium nucleatum* and *Campylobacter rectus*. The red complex includes *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*, pathogens with a high inflammatory capacity. Pathogens of the green complex, including *Eikenella corrodens* and *Capnocytophaga* spp., usually have a large local persistence and destructive potential. *Aggregatibacter actinomycetemcomitans*, of the purple complex, causes cell death and triggers inflammation through several strong virulence factors.

There is a distinct association between periodontal disease and cardiovascular diseases [8]. Possible explanations might be infectious and inflammatory mechanisms acting on the endothelium [9]. In addition, there is a well-known association between oral pathogens (mainly viridans group streptococci and HACEK pathogens, including *A.r actinomycetemcomitans*, *Haemophilus aphrophilus*, *Cardiobacterium* spp., *E. corrodens* and *Kingella kingae*) and infec-

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tive endocarditis [10]. Experimental studies suggest that endothelial damage, e.g., due to valvular and congenital abnormalities, may result in platelet-fibrin depositions and the initial formation of non-bacterial thrombotic endocardial lesions. In the presence of bacteraemia after dental interventions, microorganisms adhere to these lesions and multiply within the platelet-fibrin complex, leading to an infected vegetation and infective endocarditis [11]. Transient bacteraemia after dental interventions is dependent on the oral health and treatment modality and is found after scaling of the root surface in 25–61% and after extractions in 10–100% of patients [12]. But bacteraemia also occurs following everyday activities such as teeth brushing (13–54%), flossing (20–68%) and chewing (7–51%) [13, 14].

Infective endocarditis has an annual incidence of about 10 per 100,000 in a normal population, but this is increasing. It also has a significant associated morbidity and mortality, despite advances in diagnosis and treatment [15]. The most frequent pathogens causing infective endocarditis nowadays are non-oral pathogens such as staphylococci, followed by viridans group streptococci [16]. Prevention of bacteraemia is of utmost importance. The maintenance of good oral health and the administration of antibiotic prophylaxis before dental interventions with the potential for secondary bacteraemia, if indicated, can lower the risk of infective endocarditis due to oral pathogens [17–19]. However, the efficacy of antibiotic prophylaxis to prevent infective endocarditis has never been thoroughly investigated and clinical practice is mainly based on data extrapolated from animal models, observational studies and expert opinions [18–21]. The Swiss recommendations are based on the guidelines of the European Society of Cardiology (ESC) and include amoxicillin (cefuroxime and clindamycin in the case of allergy) in high-risk patients before periodontal treatment [18, 22].

The aim of this review, therefore, was to focus on pathogens causing bacteraemia in periodontitis patients after periodontal treatment and to match these with pathogens causing infective endocarditis in clinical practice. Based on this, the adequacy of the antibiotic prophylaxis regimen currently recommended for the prevention of infective endocarditis in periodontitis patients should be discussed. In addition, effective prevention measures to decrease the rate of bacteraemia after periodontal treatment should be analysed.

Materials and methods

This review was based on the following three questions:

1. Which pathogens are detected during bacteraemia after periodontal treatment in periodontitis patients, and is there a difference in the pathogens detected in patients with compared to without controlled periodontitis?
2. Is there a congruence of pathogens detected during bacteraemia after periodontal treatment in periodontitis patients and pathogens causing infective endocarditis in clinical practice?
3. Is the current Swiss recommendation for antibiotic prophylaxis to prevent infective endocarditis during dental interventions in high-risk cardiovascular patients adequate for patients with periodontitis?

Literature search protocols: (1) Ovid (2) EMBASE (3) Cochrane Library

The literature search was performed in the Ovid, EMBASE and Cochrane Library databases, according to the following PICO questions: (P) patients with periodontitis, (I) systemic antibiotic prophylaxis before dental intervention, (C) no systemic antibiotic prophylaxis before dental intervention, (O) bacteraemia after dental intervention. The search terms “bacteraemia”, “endocarditis”, “periodontitis”, “gingivitis”, “periodontal therapy”, “anaerobic bacteria” and “amoxicillin” were used in different combinations. “Blood infection” and “bloodstream infection” were used as synonyms for “bacteraemia”. “Valve or valvular infection” and “cardiovascular disease or infection” were used as synonyms for “endocarditis”.

The literature search included the time interval between 01 January 1990 and 31 January 2021. Only original articles written in English or German were included. Case reports, animal studies, *in vitro* studies, articles where the full text was unavailable, reviews and guidelines were excluded. The selection of the articles was done by two independent investigators (AC, MC). Due to the very scarce literature on antibiotic prophylaxis in periodontitis patients, we decided to include in our work alternative prophylactic methods to decrease bacteraemia after scaling and root planing.

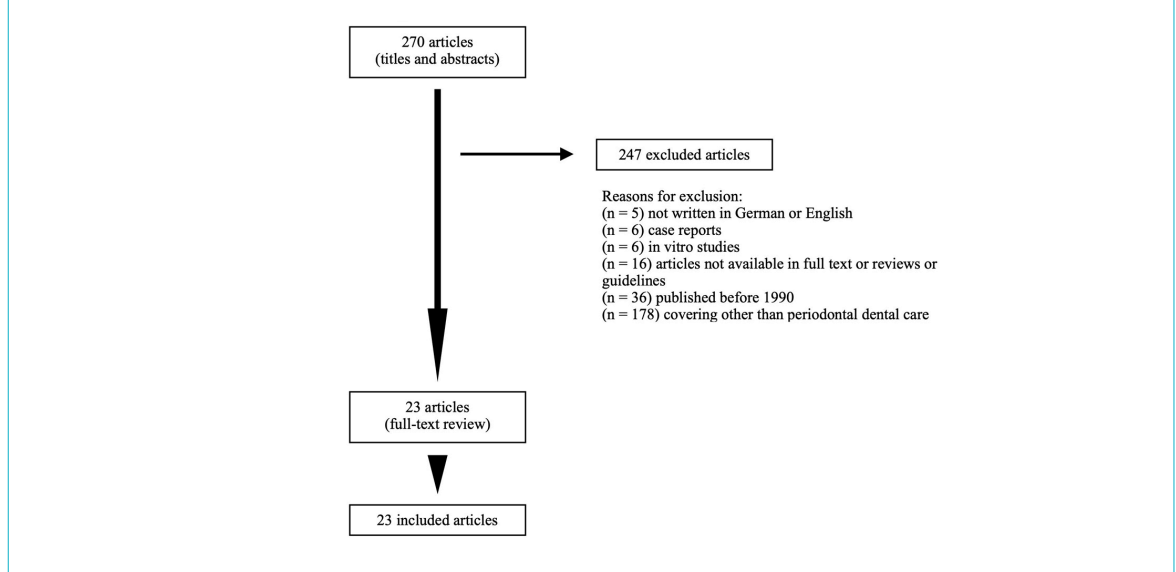
Results

Bibliographic research identified 270 articles based on titles and abstracts. After full-text review, 247 articles were excluded, resulting in 23 articles considered for this review (fig. 1). The excluded articles were either not written in English or German (n = 5), case reports (n = 6), *in vitro* studies (n = 6), articles where the full text was unavailable, reviews or guidelines (n = 16), published before 1990 (n = 36) or articles covering topics other than periodontal dental care (n = 178). Of the 23 included studies, nine articles covered the prevalence of bacteraemia, nine investigated methods to reduce bacteraemia after periodontal treatment and five analysed the rate of infective endocarditis after periodontal treatment.

Frequency and microbiology of bacteraemia after periodontal treatment

Table 1 summarises studies that assessed the frequency and microbiology of bacteraemia in periodontitis patients after periodontal treatment. Nearly all studies detected periodontal bacteria in the blood after treatment, but the frequency and composition of bacteria varied.

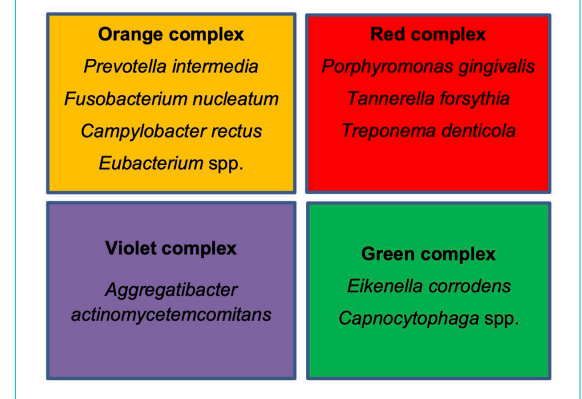
Castillo et al. detected bacteraemia with periodontal pathogens after scaling and root planing (SRP) in 55% of patients. Detection was higher by blood culture sampling (48%) than by polymerase chain reaction (PCR) (19%) [23]. Interestingly, in samples taken immediately before SRP, bacteraemia was already present in 17% of the patients. *P.s. gingivalis* was the most commonly isolated pathogen, in 50% of patients, followed by *A.r. actinomycetemcomitans* in 21%, along with other members of the different bacterial complexes that are involved in periodontal destruction (fig. 2). Forner et al. found bacteraemia rates after scaling of 10%, 20% and 75% in three groups of 20 individuals with good oral health, gingivitis and pe-

Figure 1: Selection of the studies: number of screened, included and excluded studies.

riodontitis respectively. The bacteraemia rate was significantly higher in the patients with periodontitis. Blood cultures mostly detected viridans group streptococci, followed by *Prevotella* and *Fusobacterium* spp. [24]. Another study by the same group evaluated bacteraemia after scaling in 20 individuals with untreated periodontitis. Bacteraemia was detected in 75% after 30 seconds, in 35% after 10 minutes and in 10% after 30 minutes, mostly with streptococci and gram-negative bacilli [25]. Kinane et al. evaluated the incidence of bacteraemia following ultrasonic scaling in 30 patients with periodontal disease. Bacteraemia was detected by PCR in 23% of the patients, with *Actinomyces naeslundii* and viridans group streptococci dominating [26]. In Lafaurie's study, bacteraemia was found in 94% of patients suffering from generalised aggressive periodontitis and in 74% of patients suffering from severe generalised chronic periodontitis, without a significant difference between these two groups. The highest incidence of bacteraemia was found immediately after SRP, but 19% were still bacteraemic 30 minutes after the procedure, with *P.s gingivalis*, *Micromonas micros* and *Actinomyces* spp. the most frequently isolated pathogens [27]. Perez et al. only evaluated bacteraemia for *P.s gingivalis*, which was detected in 6 out of 15 periodontitis patients (40%) after SRP [28, 29]. Amongst 40 chronic periodontitis patients, Waghmare et al. detected bacteraemia in 8% before, in 70% immediately after and in 25% 30 minutes after SRP. The most commonly isolated periodontopathic pathogens were *P.s gingivalis* (38%), *M. micros* (23%), *P. intermedia* (15%), *T. forsythia* and *Eikenella corrodens* (13% each) and *Campylobacter* spp. (8%) [30]. In Zhang's study, the incidence of bacteraemia after flossing and periodontal treatment was analysed in 30 patients with chronic periodontitis. Bacteraemia was detected after SRP in 43% of the patients. *Actinomyces* spp. dominated and were in 37% of the samples after SRP. Viridans group streptococci were detected in 27% of the cases, followed by *Prevotella* spp. and *Fusobacterium* spp. [31].

Microbiological differences in bacteraemia after periodontal treatment in healthy individuals and in patients with gingivitis and periodontitis

The quantity and types of pathogens isolated from blood were different between healthy individuals and patients with gingivitis or periodontitis: of the 60 patients in Forner's study, 20 were healthy, 20 suffered from gingivitis and 20 suffered from periodontitis [24]. Blood cultures were drawn after chewing, teeth brushing and periodontal treatment with scaling. The incidence of bacteraemia after scaling was 10% in healthy individuals, significantly lower than the 20% and 75% in patients with gingivitis and periodontitis respectively. Only 5% and 20% of the periodontitis patients had positive blood cultures after chewing and toothbrushing respectively. No patients in the other two groups had bacteraemia after either of these activities, however this difference was not significant. The majority of bacteraemia episodes cleared within 30 minutes and included, for the gingivitis and periodontitis patients, pre-

Figure 2: Bacterial complexes in periodontitis. The colours indicate different pathogen groups in the development of periodontitis. The orange complex includes pathogens important to the initiation of periodontal disease. The red complex includes pathogens with a highly inflammatory capacity. Pathogens of the green complex usually have a high local persistence and destruction potential and pathogens of the purple complex have several strong virulence factors that cause cell death and trigger or evade inflammation.

dominantly viridans group streptococci and other streptococci, as well as *Prevotella* and *Fusobacterium* spp., although the latter two pathogens were more prevalent in gingivitis patients, in addition to the presence of *P.s. gingivalis*.

Risk of infective endocarditis in patients with predisposing cardiac conditions and dental interventions

Chirillo et al. examined 677 patients from the Italian Registry of Infective Endocarditis in a retrospective cohort study. Out of 111 patients with a predisposing heart condition (e.g., prosthetic valves) and an interventional procedure before the occurrence of infective endocarditis, only 20 patients had received dental treatment within the previous two months. In eight of these 20 patients infective endocarditis was caused by viridans group streptococci, while in the others it was caused by *enterococci*, *S. aureus* or *S. epidermidis* [32].

Intentional methods to reduce bacteraemia rates during periodontal treatment

Table 2 summarises different methods to reduce bacteraemia rates during dental interventions, including SRP.

Chlorhexidine

Allison et al. compared oral rinsing with chlorhexidine 0.12% and with a placebo (water) before periodontal treatment in two groups of 12 patients with periodontitis. The incidence of post-interventional bacteraemia was significantly lower, at 25%, in the chlorhexidine group, compared to 75% in the control group; viridans group streptococci dominated [33]. In another report on 27 periodontitis and 26 gingivitis patients receiving oral rinsing with chlorhexidine 0.12% before periodontal therapy, the bacteraemia rate was significantly higher in the periodontitis

Table 1:
Frequency and microbiology of bacteraemia after periodontal treatment.

Author	Dental pathology (n = sample size)	Incidence of bacteraemia	Dental treatment	Microbiological method	Overall microbiology after scaling and root planing in periodontitis and gingivitis patients
Castillo et al. 2011	Periodontitis (n = 42)	55% (23/42)	Scaling and root planing	Blood culture, PCR	<i>Porphyromonas gingivalis</i> (50%), <i>Aggregatibacter</i> spp. (21%), <i>Porphyromonas micra</i> (17%), <i>Campylobacter rectus</i> (16%), <i>Tannerella forsythia</i> (12%), <i>Eikenella corrodens</i> (10%), <i>Prevotella intermedia</i> (7%)
	Aggressive periodontitis (n = 15)	53% (8/15)			
	Chronic periodontitis (n = 27)	52% (14/27)			
Fornier et al. 2006	Healthy individuals (n = 20)	10% (2/20)	Scaling	Blood culture after lysis filtration method	Viridans group streptococci (43%), <i>Prevotella</i> spp. (23%), <i>Fusobacterium nucleatum</i> (18%), <i>Porphyromonas gingivalis</i> (5%), <i>Actinomyces</i> spp. (3%), <i>Corynebacterium</i> spp. (3%), <i>Lactobacillus</i> spp. (3%)
	Gingivitis (n = 20)	20% (4/20)	Scaling		
	Periodontitis (n = 20)	75% (15/20)	Scaling and root planing		
Fornier et al. 2006	Periodontitis (n = 20)	75% (at 0.5 min.) (15/20)	Scaling and root planing	Blood culture after lysis filtration method	Viridans group streptococci (65%), <i>Prevotella</i> spp. (40%), <i>Fusobacterium nucleatum</i> (30%), <i>Porphyromonas gingivalis</i> (10%), <i>Actinomyces</i> spp. (5%), <i>Lactobacillus</i> spp. (5%), <i>Corynebacterium</i> spp. (5%)
		35% (at 10 min.) (7/20)			
		10% (at 30 min.) (2/20)			
Kinane et al. 2006	Untreated periodontal disease (n = 30)	23% (7/30)	Scaling and root planing	Blood culture, PCR	<i>Actinomyces naeslundii</i> (6%), <i>Streptococcus parasanguinis</i> (3%), <i>Eubacterium</i> spp. (3%), <i>Cutibacterium acnes</i> (3%)
Lafaurie et al. 2007	Periodontitis (n = 42)	81% (34/42)	Scaling and root planing	Blood culture	<i>Porphyromonas gingivalis</i> (29%), <i>Actinomyces</i> spp. (29%), <i>Prevotella</i> spp. (19%), <i>Micromonas micros</i> (17%), <i>Campylobacter</i> spp. (12%), <i>Capnocytophaga</i> spp. (12%), <i>Fusobacterium</i> spp. (12%), <i>Cutibacterium acnes</i> (12%), <i>Eikenella corrodens</i> (10%), <i>Tannerella forsythia</i> (7%), <i>Bifidobacterium</i> spp. (5%), <i>Eubacterium aerofaciens</i> (2%), <i>Gemella morbillorum</i> (2%)
	Aggressive periodontitis (n = 15)	94% (14/15)			
	Chronic periodontitis (n = 27)	74% (20/27)			
Perez et al. 2008	Periodontitis (n=16)	44% (7/16)	Scaling and root planing	Blood culture, PCR	Blood cultures only analyzed for <i>Porphyromonas gingivalis</i>
Perez et al. 2009	Periodontitis (n=15)	40% (6/15)	Scaling and root planing	Blood culture, PCR	Blood cultures only analyzed for <i>Porphyromonas gingivalis</i>
Waghmare et al. 2013	Periodontitis (n = 40)	70% (28/40)	Scaling and root planing	Blood culture	<i>Porphyromonas gingivalis</i> (38%), <i>Micromonas micros</i> (23%), <i>Prevotella intermedia</i> (15%), <i>Tannerella forsythia</i> (13%), <i>Micromonas micros</i> (23%), <i>Prevotella intermedia</i> (15%), <i>Tannerella forsythia</i> (13%), <i>Eikenella corrodens</i> (13%), <i>Campylobacter</i> spp. (8%)
Zhang et al. 2013	Periodontitis (n = 30)	43% (13/30)	Scaling and root planing	Blood culture	<i>Actinomyces</i> spp. (37%), Viridans group streptococci (27%), <i>Prevotella</i> spp. (24%), <i>Peptostreptococcus</i> spp. (14%), Anaerobic gram-negative rods (7%), <i>Fusobacterium</i> spp. (4%), Milleri group streptococci (3%), <i>Veillonella</i> spp. (3%), <i>Corynebacterium</i> spp. (2%), <i>Rothia</i> spp. (0.4%), <i>Moraxella</i> spp. (0.4%)

PCR: polymerase chain reaction

¹ Frequency determined as the number of patients with positive blood cultures for the respective pathogen out of all patients with blood culture sampling in the respective group. Polymicrobial bacteraemia was detected in many patients, and in these every pathogen was counted individually. Data do not include microbiology of healthy individuals.

patients and included mainly *P.s gingivalis*. However, pre-procedural rinsing had no significant effect on the bacteraemia rate compared to no rinsing [34]. In Loftus' study, a single professional subgingival irrigation with chlorhexidine 0.12% was compared with water rinsing in patients receiving SRP. Bacteraemia with mainly Gram-positive pathogens was detected in 20% of patients in the chlorhex-

idine group, compared to 40% in the control group. However, this difference was not significant [35].

Povidone-iodine (PVP-iodine)

In a randomised, placebo-controlled trial with sixty gingivitis patients, half of the patients rinsed with saline 0.9% and the other half with PVP-iodine 7.5% for two minutes.

Table 2:

Measures to decrease the risk of bacteraemia after periodontal treatment and pathogen distribution in cases of bacteraemia

Author	Dental pathology (n = sample size)	Preventive agent	Comparator	Incidence of bacteraemia (preventive agent / comparator)	Microbiology after scaling and root planing in preventive agent group ¹	Microbiology after scaling and root planing in comparator group ¹
Allison et al. 1993	Periodontitis (n = 24)	Chlorhexidine 0.12% (n = 12)	Placebo (n = 12)	25% (3/12) / 75% (9/12)*	Viridans group streptococci (17%), <i>Corynebacterium</i> spp. (17%), non-haemolytic streptococci (8%), <i>Bacteroides</i> spp. (8%), <i>Fusobacterium</i> spp. (8%), <i>Moraxella</i> spp. (8%), <i>Cutibacterium</i> spp. (8%)	Viridans group streptococci (42%), <i>Eikenella</i> spp. (17%), <i>Peptostreptococcus</i> spp. (8%), Milleri group streptococci (8%), <i>Fusobacterium</i> spp. (8%), <i>Corynebacterium</i> spp. (8%), <i>Pasteurella</i> spp. (8%), anaerobic gram-positive cocci (8%), microaerophilic gram-positive bacteria (8%)
Loftus et al. 1991	Periodontitis (n = 30)	Chlorhexidine 0.12% (n = 10)	Sterile water (n = 10) No irrigation (n = 10)	20% (2/10) / 40% (4/10) 20% (2/10) / 30% (3/10)	Not specified	Not specified
Balejo et al. 2017	Gingivitis and periodontitis (n = 53)	Chlorhexidine 0.12% (n=26)	No rinse (n = 27)	Similar quantitative PCR levels (frequency not specified)	Not specified	Not specified
Cherry et al. 2007	Gingivitis (n = 60)	Povidone-iodine 7.5% (n = 30)	0.9% saline water (n = 30)	10% (3/30) / 33% (10/30)*	<i>Enterobacteriaceae</i> (10%)	<i>Prevotella intermedia</i> (17%), Viridans group streptococci (13%), Milleri group streptococci (10%), <i>Actinomyces</i> spp. (7%), <i>Porphyromonas gingivalis</i> (3%), <i>Streptomyces</i> spp. (3%), Gram-positive cocci (3%)
Sahrmann et al. 2015	Periodontitis (n = 38)	Povidone-iodine 10% (n = 19)	0.9% saline water (n = 19)	26% (5/19) / 58% (11/19)*	Viridans group streptococci (11%), <i>Rothia dentocariosa</i> (5%), <i>Corynebacterium accolens</i> (5%)	<i>Parvimonas micra</i> (32%), Milleri group streptococci (21%), <i>Fusobacterium</i> spp. (16%), <i>Actinomyces</i> spp. (16%), Viridans group streptococci (11%), <i>Prevotella intermedia</i> (11%), anaerobe gram-negative rods (11%), anaerobe gram-positive rods (11%), anaerobe gram-positive cocci (11%), <i>Aggregatibacter actinomycetemcomitans</i> (5%), <i>Veillonella</i> spp. (5%), <i>Porphyromonas gingivalis</i> (5%), <i>Clostridium</i> spp. (5%), <i>Lactobacillus</i> spp. (5%)
Fine et al. 1996	Gingivitis and periodontitis (n = 36)	Essential oil (Listerine®) (n = 18)	5% hydro-alcohol (n = 18)	92% lower aerobic and 87% lower anaerobe colony count in preventive agent group*	Not specified	Not specified
Assaf et al. 2007	Gingivitis (n = 44)	Diode laser (n = 22)	No diode laser (n = 22)	36% (8/22) / 68% (15/22)*	Viridans group streptococci (27%), <i>Prevotella melaninogenica</i> (9%), <i>Haemophilus</i> spp. (5%), <i>Fusobacterium</i> spp. (5%), <i>Capnocytophaga</i> spp. (5%), <i>Bacteroides</i> spp. (5%)	Viridans group streptococci (50%), <i>Prevotella intermedia</i> (27%), <i>Capnocytophaga</i> spp. (9%), <i>Haemophilus</i> spp. (5%), <i>Bacteroides</i> spp. (5%), unidentified gram-positive bacilli (5%)
Morozumi et al. 2010	Periodontitis (n = 30)	Azithromycin, oral (1x500 mg per day 3 days before intervention) (n = 10)	Essential oil (Listerine®) (n = 10) No intervention (n = 10)	20% (2/10) / 70% (7/10)* / 20% (2/10) / 90% (9/10)*	Viridans group streptococci (10%), <i>Actinomyces</i> spp. (10%)	<i>Parvimonas micra</i> (30%), <i>Fusobacterium nucleatum</i> (20%), Viridans group streptococci (10%), <i>Peptostreptococcus anaerobius</i> (10%), <i>Eubacterium</i> spp. (10%), <i>Eggerthella lenta</i> (10%), <i>Cutibacterium acnes</i> (10%) Viridans group streptococci (70%), beta-haemolytic streptococci (10%), Milleri group streptococci (10%)
Reis et al. 2017	Periodontitis (n = 55)	Amoxicillin, oral (1x2 g) (n = 24)	No Amoxicillin (n = 31)	17% (4/24) / 23% (7/31) (at 5 min. after scaling) 8% (2/24) / 16% (5/31) (at 30 min. after scaling)	Not specified	Not specified

PCR: polymerase chain reaction

¹ Frequency determined as the number of patients with positive blood cultures for the respective pathogen out of all patients with blood culture sampling in the respective group. Polymicrobial bacteraemia was detected in many patients, and in these every pathogen was counted individually.

* Significant difference

PVP-iodine reduced the incidence and magnitude of bacteraemia and eliminated viridans group streptococci (10% versus 33%), corresponding to an odds ratio (OR) of 0.19 (95% confidence interval [CI] 0.04–0.83) for bacteraemia. Additionally, periodontal pathogens including *P. intermedia* and *P.s. gingivalis* were eliminated [36]. Similar findings were shown by Sahrman et al. when subgingival instrumentation was performed after rinsing with PVP-iodine 10% or water in patients with periodontitis. A significantly lower incidence of bacteraemia of 26% was documented in the test group, compared to 58% in the control group [37].

Essential oils

In 25 patients with gingivitis or periodontitis, mouth rinsing and subgingival irrigation with an antiseptic essential oil (Listerine®) was performed before ultrasonic scaling. The antiseptic mouth rinse and irrigation resulted in a 92% lower aerobic and an 88% lower anaerobic count of pathogens causing bacteraemia compared to control patients. These differences were significant [38].

Laser

By applying a diode laser instead of the use of ultrasonic scaling in 22 gingivitis patients, the post-interventional bacteraemia rate was significantly reduced, from 68% to 36%. A wide range of microorganisms of the oral microbiome were isolated in blood cultures, but viridans group streptococci dominated (50%) [39].

Antibiotic prophylaxis

In a randomised study including 30 patients suffering from chronic periodontitis, three groups were compared: irrigation with essential oil, intake of oral azithromycin before SRP and a control group. Subgingival irrigation with essential oil was administered and continued at home for a week and oral azithromycin (500 mg daily) was started three days before the intervention. Bacteraemia rates were 70% (essential oil), 20% (azithromycin) and 90% (control group), which was a significant reduction for the azithromycin group. More than half of the microorganisms isolated in blood cultures were streptococci, followed by *P. micra* and *F. nucleatum*. Periodontopathogens of the so-called red and violet complexes were rarely detected (fig. 2) [40]. Reis et al. analysed antibiotic prophylaxis with amoxicillin (2 g before dental extraction and supragingival scaling) in 44 patients at high risk for infective endocarditis according to the Brazilian Cardiology Society guidelines. These patients were compared to 51 low-risk patients without prophylaxis. Blood cultures were taken prior to, 5 and 30 minutes after the intervention. Bacteraemia was detected by quantitative PCR in 23% after 5 minutes and in 16% after 30 minutes in low-risk patients without prophylaxis, and in 17% and 8% after 5 and 30 minutes, respectively, in high-risk patients with prophylaxis, which was not a significant difference. When using blood cultures instead of PCR, the sensitivity was lower and bacteraemia was detected in 6% after 5 minutes and 0% after 30 minutes in low-risk patients, and in 4% and 0% after 5 and 30 minutes, respectively, in patients at high risk for infective endocarditis with prophylaxis, which again was not a

significant difference. Besides viridans group streptococci, pathogens associated with periodontal disease such as *P.s. gingivalis* and *F. nucleatum* were isolated [41].

Discussion

This literature review was performed to update and reconsider the adequacy of the antibiotic prophylaxis regimen currently recommended for the prevention of infective endocarditis in high-risk cardiovascular patients receiving periodontal treatment in dental practice, as many pathogens causing bacteraemia after periodontal intervention are not covered by the recommended prophylaxis with amoxicillin. The clinical relevance of these pathogens was analysed, and they were matched with those causing infective endocarditis in clinical practice. Additionally, the effect of locally applied antiseptic methods on bacteraemia episodes in periodontal treatment was analysed.

A wide variety of oral pathogens are found during bacteraemia in patients being treated for gingivitis and periodontitis [23–27, 30, 31, 33–43]. This includes pathogens causing infective endocarditis in clinical practice, such as viridans group streptococci, HACEK group pathogens and *Prevotella* spp., but also pathogens not usually associated with infective endocarditis, such as *P.s. gingivalis*, *Actinomyces* spp., *Treponema* spp. and *Fusobacterium* spp., amongst others [44]. Additionally, gingivitis and periodontitis patients have a broader microbiological spectrum and a higher incidence of bacteraemia than healthy individuals [24, 25, 32, 45]. This can be explained by a higher microbiological density, but also by the inflamed gingiva in periodontitis, which predisposes them to bleeding and therefore bacteraemia. The rate of bacteraemia after periodontal treatment was between 23% and 94%, depending on the time of blood culture collection after treatment, the methods used (blood culture versus PCR) and the severity of periodontitis [26, 27]. Interestingly, some periodontal patients were bacteraemic even before the intervention started, supporting the hypothesis of the relevance of the higher microbiological load and inflamed gingiva in these patients [23].

From a clinical point of view, there is a discrepancy between the wide variety of pathogens involved in periodontitis and causing bacteraemia after periodontal treatment and the oral pathogens causing infective endocarditis in clinical practice. Other than viridans group streptococci, oral pathogens only rarely cause infective endocarditis. HACEK group pathogens, the second most common after viridans group streptococci, account for only 3% of infective endocarditis cases [16, 17, 44]. Both pathogen groups are present in dental biofilms in patients with periodontitis, but are not the most aggressive in terms of triggering the mechanisms of periodontal destruction (except for *A.r. actinomycetemcomitans* of the HACEK group). Possible explanations for this discrepancy could be differences in the adherence potential to vegetations and in the microbial density and duration of bacteraemia, but also the possibility that the blood milieu does not convene to all pathogens to the same extent. In recent years there has been an epidemiological and microbiological change in infective endocarditis. Thirty to forty years ago, viridans group streptococci dominated in infective endocarditis. Nowadays, staphylococci account for >50% of all infective endocardi-

tis episodes and streptococcal infective endocarditis has significantly decreased to about 20% of cases [16]. Staphylococci usually originate from skin or vascular catheters, but rarely from the oral cavity, which is congruent with the finding that they are rarely isolated in patients with periodontal disease. The staphylococcal dominance is explained by the changing patient population, which today is older, more polymorbid and has more healthcare contacts and intravascular devices such cardiovascular implantable electronic devices and tunnelled catheters for haemodialysis or chemotherapies, all of which predispose patients to infections with *S. aureus* and coagulase-negative staphylococci [16, 17, 44].

To reduce the risk and also the variety of bacteraemia after periodontal treatment, different non-antibiotic intervention strategies are proposed. The most promising agents are chlorhexidine (0.12%) and PVP-iodine (7.5%/10%). Chlorhexidine 0.12% decreased bacteraemia with mainly viridans group streptococci from 75% to 25% [33], PVP-iodine 7.5% from 33% to 10% and PVP-iodine 10% from 58% to 26% [36, 37]. Although mouth rinses are convenient to use, it must be mentioned that regular rinsing with chlorhexidine might discolour teeth and reduce taste sensation. Therefore, antiseptic mouth rinsing with essential oil (Listerine®) or the use of a diode laser might be alternatives for lowering bacteraemia rates [38, 39].

Antibiotic prophylaxis before dental interventions to prevent infective endocarditis in high-risk cardiovascular patients is controversial, as evidence is low and based on heterogeneous studies, often of poor methodological quality (including animal models, observational studies and expert opinions) [46]. The most important limitation of studies describing bacteraemia after periodontal treatment is the misleading endpoint. Bacteraemia alone is not a clinically relevant surrogate endpoint and does not correlate with infective endocarditis. Studies by Morozumi et al. and Reis et al. do indeed describe a reduced bacteraemia rate after a three-day course of oral azithromycin or a single dose of amoxicillin before SRP, but there is no information about infective endocarditis events thereafter [40, 41]. A few retrospective studies chose infective endocarditis as the clinical endpoint and found that more intensive and frequent periodontal treatment in patients at risk for infective endocarditis optimised oral health and was associated with a reduced risk of infective endocarditis [45, 47]. The presumed infective endocarditis incidence after 12 weeks was 3.9% for dental scaling and 2.4% for periodontal treatment [48]. Similarly, only 4.7% of dental procedures were supposed to be causal for infective endocarditis [32]. In a retrospective study by Martin et al., a 15% chance of developing infective endocarditis after scaling was suggested if no antibiotic prophylaxis was applied [49]. However, patients receiving antibiotic prophylaxis can also develop infective endocarditis, which was the case in 4 out of 20 patients with a predisposing heart condition suffering from infective endocarditis by viridans group streptococci despite a prophylaxis (3 g amoxicillin single dose) being taken before the intervention [32]. In any case, causality is difficult to prove in all those retrospective studies, especially as regular daily activities such as chewing or teeth brushing cause multiple daily bacteraemia episodes, and in the worst cases infective endocarditis [23, 24, 45, 48, 50]. This is al-

so underlined by the fact that many periodontal patients were bacteraemic even before the intervention started [23]. Despite limited evidence, the ESC and the American Heart Association (AHA) recommend prophylaxis for high-risk patients to help avoid the devastating complication of infective endocarditis [18, 19]. The British National Institute for Health and Clinical Excellence (NICE) abandoned dental prophylaxis in 2008, not only because of limited evidence, but also because of considerable costs, possible side effects (including allergic reactions and *Clostridioides difficile*-associated colitis) and the risk of selecting for antibiotic resistance in pathogens [51, 52]. After this intervention, there was an 89% reduction in prescribing antibiotic prophylaxis for infective endocarditis, but over the following five years there was a significant increase in infective endocarditis cases per month (0.11 cases per 10 million people per month; 95% CI 0.05–0.16, $p < 0.0001$) [53]. Nevertheless, here causality is also not proven because the pathogen spectrum causing those additional infective endocarditis episodes is unknown and too many confounders are involved. The latter include factors increasing the prevalence of patients at risk for infective endocarditis (age, comorbidity, patients migrating from countries with a higher prevalence of rheumatic heart disease and worse oral health), but also possible changes in how oral health is propagated and maintained and more sensitive methods for diagnosing infective endocarditis. Currently, NICE states that regular antibiotic prophylaxis is still not recommended but might be considered in individual patients [54]. The Swiss recommendations are based on the ESC guidelines and recommend oral amoxicillin (cefuroxime or clindamycin in case of allergy) before certain dental interventions in patients at high risk for infective endocarditis [22]. This strategy can be supported, as amoxicillin has a low rate of side effects, little collateral damage due to its narrow spectrum of activity and a low non-susceptibility rate of viridans group streptococci (0.2–1.4%), the dominant infective endocarditis-associated pathogen from the oral cavity [55, 56].

The main limitation when discussing the adequacy of antibiotic prophylaxis is the fact that most studies chose bacteraemia after periodontal treatment as the primary outcome, which is a poor surrogate endpoint for infective endocarditis with limited clinical relevance. The methods used to detect bacteraemia differed between the studies and included PCR and blood cultures. It can be supposed that the more sensitive PCR also detects low-level, clinically irrelevant bacteraemia. Therefore, it would be interesting to know whether patients with only a positive PCR test had the same infective endocarditis risk as patients with a positive blood culture test. Nevertheless, this narrative review gives a broad overview of the pathogens detected in bacteraemia after periodontal treatment and highlights the different strategies to prevent them.

In conclusion, a wide range of pathogens cause bacteraemia after periodontal therapy, but only viridans group streptococci and, at a much lower rate, HACEK group pathogens seem clinically relevant for causing infective endocarditis. Because of the low non-susceptibility rate of viridans group streptococci to and the good tolerance of amoxicillin, with little collateral damage due to its narrow spectrum, the prophylactic recommendation before certain

dental interventions remains adequate. As more resistant periodontal pathogens are only rarely clinically relevant for infective endocarditis and the overall evidence for the efficacy of prophylaxis is limited, a broader antibiotic prophylaxis is not justified by the small number of patients who might benefit from a prophylactic point of view, at the expense of more side effects and the development of resistance. There are other effective measures to reduce bacteraemia episodes after periodontal treatment, namely antiseptic mouth rinsing before treatment and raising awareness of daily oral hygiene. To reduce the frequency of antibiotic prophylaxis administration in periodontitis patients at high risk for infective endocarditis, efficient treatment planning and a reduced number of appointments are relevant. This probably prevents more episodes of infective endocarditis and is a more global prevention strategy.

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