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ORIGINAL ARTICLE

Radiography-based score indicative for the pathogenicity of bacteria in odontogenic infections

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Abstract

Objective. To develop a new radiography-based score to assess the potential of bacteria to cause odontogenic infections derived from the occurrence of bacteria at small or large radiographical lesions. ***Materials and methods.*** The patients analyzed were a sub-population from a large randomized clinical trial comparing moxifloxacin and clindamycin in the treatment of inflammatory infiltrates and odontogenic abscesses. Routine radiographs were used to analyze the area of the periapical radiolucent lesions. Lesions were stratified by their radiographically measured area as large (>9 mm^2) or small (≤9 mm^2). A risk ratio was calculated for each species from the frequency of their occurrence in large vs in small lesions. ***Results.*** Fifty-one patients, 19 with abscesses and 32 with infiltrates, were evaluated. Overall, the radiographical lesion areas ranged from 0.4–46.2 mm^2 (median = 9 mm^2). An increased risk (risk ratio >1) to occur at large abscess lesions was observed for *Prevotella* (*P.*) *oralis, P. buccae, P. oris, P. intermedia, Fusobacterium nucleatum and Streptococcus* (*Strep.*) *anginosus* group. An increased risk to occur at large infiltrate lesions was found for *Strep. salivarius, Strep. parasanguis, Strep. anginosus* group, *Capnocytophaga* spp., *Neisseria* (*N.*) *sicca, Neisseria* spp., *Staphylococcus (Staph.) aureus, P. intermedia, P. buccae, Prevotella* spp. and *P. melaninogenica*. ***Conclusions.*** The radiography-based score suggests that certain *Prevotella* spp., *F. nucleatum* and *Strep. anginosus* groups play a crucial role in the pathogenesis of odontogenic abscesses, and that various streptococci, *Neisseria* spp., *Capnocytophaga* spp., *Staph. aureus* and *Prevotella* spp. are involved in the pathogenesis of odontogenic infiltrates.

Key Words: *antibiotics, bacterial isolates, periapical radiolucent lesions, X-ray*

Introduction

Infections of the maxillofacial region are often of odontogenic origin and caused by a mixed flora of aerobic, facultative anaerobic and anaerobic bacteria [1,2]. The microbiota show facultative anaerobes as viridans group streptococci and streptococcus anginosus group. Other predominant pathogens are strictly anaerobe bacteria such as *Prevotella* and *Fusobacterium* species [3–6]. In odontogenic abscesses typically three to six different bacterial species are present [7]. Odontogenic infections are the most prevalent infectious diseases within the maxillofacial region [8,9]. They may result in cellulitis or abscesses and may lead to serious complications [10]. The management of these infections should be based on the severity of the clinical course and represents a challenge to general dental practitioners and oral/maxillofacial surgeons [11]. Due to the polymicrobial etiology of odontogenic infections the use of broad spectrum antibiotics is advisable. For most minor infections sensitivity testing of the involved microorganisms is not performed routinely, as local treatment and empirical therapy with antibiotics substantially resolve the infection in most cases. Nevertheless, a microbiological assessment is mandatory in severe courses as well as in patients not responding to anti-infective therapy.

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However, the time required for species identification and susceptibility testing of the isolates may delay the initiation of appropriate antimicrobial therapy. This may lead to a progression of the disease process and result in increased healthcare costs due to hospitalization and extended length of hospital stay [11]. To avoid such a course, it is desirable to obtain information about the likely pathogens as early as possible. The aim of this investigation was, therefore, to assess potential correlations between the radiographic sizes of the lesions in patients with odontogenic infections and the occurrence and pathogenicity of specific bacteria in these infections. A strong correlation might provide the opportunity to eventually predict the disease process, supplemented by the clinical evaluation, prior to collecting of microbiological samples for culture analyses and thereby to gain time for an early appropriate antimicrobial therapy.

Materials and methods

Patients

The patients analyzed in this study were a subpopulation out of a prospective, double-blind, randomized clinical trial performed to compare the efficacy and safety of moxifloxacin vs clindamycin in the treatment of outpatients with odontogenic infections. Patients had a diagnosis of gingival inflammatory infiltrates requiring medical therapy including an antibiotic or a diagnosis of an odontogenic abscess (dentoalveolar or periodontal) requiring surgical intervention with adjunctive antibiotic treatment. Detailed clinical and microbiological results as well as inclusion and exclusion criteria are described elsewhere [12,13].

After approval by the Ethics Committee, a total of 51 patients with either inflammatory infiltrates or odontogenic abscesses attending the ambulatory care unit of the Department of Restorative and Preventive Dentistry (University Medical Center Hamburg-Eppendorf) were randomly selected. Written informed consent was obtained from all subjects.

The data of the current analysis are based upon routine radiological imaging obtained at baseline prior to any anti-infective therapy.

Microbiological sample collection

Prior to sample collection, the mucosa over each inflammatory infiltrate or abscess was cleaned with sterile cotton gauze and disinfected by 1.1% povidone-iodine (Betaisodona™, Mundipharma GmbH, Limburg, Germany) as pre-surgical antiseptic to avoid salivary contamination. At the initial visit, prior to antimicrobial therapy, swabs were taken of sanguineous exudates or pus, respectively, by puncture or incision, placed in Amies charcoal medium (BBL™ CultureSwab™, Becton Dickinson Inc., Heidelberg, Germany), and cultured within 24 h of collection.

Columbia agar plus 5% sheep blood and Schaedler agar were used for cultivation of aerobes/facultative anaerobes and anaerobes, respectively. All bacterial isolates were identified at the species level using the VITEK™ 2 system (bioMérieux, Nürtingen, Germany) according to manufacturer's instructions. The MICs of penicillin (PEN), amoxicillin/clavulanic acid (AMC), clindamycin (CLI), doxycycline (DOX), levofloxacin (LVX) and moxifloxacin (MXF) were determined by Etest (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions.

Radiographic examination

Standardized conventional radiographs were taken at baseline, prior to therapy and for diagnostical reasons, of each patient consecutively using film-holding devices (Dentsply Rinn, Inc., Konstanz, Germany) for the paralleling technique performed with a long cone of 30 mm. The appropriate Rinn XCP™ holder and the size of the film packet were selected according to the region of the teeth. For incisors and canines an anterior holder with a film packet of 22 $\times$ 35 mm was applied and for the posterior region (premolars and molars) the corresponding holder with a film packet of 31 $\times$ 41 mm was used. Dental X-ray film positioning devices were used to enhance dimensional accuracy of X-ray images and their reliability [14].

The radiographs were obtained using an intra oral X-ray generator Heliodent DS (Sirona Dental Systems, Inc., Bensheim, Germany). Exposure parameters were 60 kV, 7 mA and varying times depending on the examined tooth area. Kodak Insight film IP-22 sized #2 (Eastman Kodak Co., Rochester, NY) was used with an exposure time of 0.16 s for incisors, canines and premolars, 0.20 s for molars and 0.25 s for second and third maxillary molars. All exposure times were in accordance with manufacturer's recommendations. All conventional films were processed under identical conditions in an X-ray automatic processor machine (XR 24-II, Dürr Dental, Bietigheim-Bissingen, Germany), digitized in a flatbed scanner using imaging software SilverFast Ai V 6.0.1r16 (Lasersoft Imaging, Inc., Kiel, Germany) and saved in 16-bit TIF file format with a resolution of 600 dpi according to a method briefly described by Wicht et al. [15].

Radiographic image processing and measurements

Each of the images was evaluated independently by three experienced examiners, a dental radiologist (U. R.), a general dental practitioner (G.C.) and a maxillofacial surgeon (M.B.). Before evaluation all images were calibrated. A region of interest (ROI) was selected from X-rays with periapical radiolucencies, including periodontal and pericoronal spaces, respectively, when pathologically widened. In accordance with results by Britto et al. [16], a root with an apical periodontal ligament no wider than twice the width of the rest of the periodontal ligament was regarded as radiographically adequate. The documented radiolucencies were also based on the apical periodontium status which was assessed by a 5-score periapical index (PAI) described by Ørstavik et al. [17].

The images were saved in uncompressed TIF format and were evaluated with the validated Java-based open source ImageJ software version 1.42j (Wayne Rasband, National Institutes of Health, Bethesda, MD, freeware from http://rsb.info.nih.gov/ij/) for further measurements [15,18,19]. For the measurements of the ROI, a calibration by set scale was performed. The lesion areas were calculated using the ROI manager. Plugins were not implemented, as no analysis of grayscale images was required. When the pixel count (ppi) was indicated in millimeters, a division by 25.4 was required according to manufacturer's instructions.

Correlation of microbial isolates with radiological findings (score development)

Bacteria occurring more frequently in larger odontogenic lesions were considered to be more pathogenic than bacteria predominantly isolated from smaller lesions. Based on this premise, the aim of the study was to assess the potential of bacteria to cause odontogenic abscesses or infiltrates from their occurrence in large or small lesions. To classify the pathogenicity, a risk ratio was calculated—separately for abscess and for infiltrate lesions—as the quotient of the frequency of each bacterial species' occurrence in large lesions vs in small lesions. A risk ratio >1 was considered to be increased.

Results

Analysis of the study population

The study population consisted of 32 male and 19 female patients. The mean age was 44.2 years (SD = 15.4, range = 20–85). Of the 51 patients, 19 had an abscess diagnosis and 32 had an infiltrate diagnosis. Odontogenic swabs were obtained from all 51 patients and yielded 158 bacterial isolates. After exclusion of species with single occurrence, 144 isolates remained for further analysis. Of these, 60 were isolates from patients with abscesses and 84 were isolates from patients with infiltrates. Abscesses and infiltrates had polymicrobial etiology in 95% and 84% of cases, with an average number of 3.2 and 2.6 isolates per specimen, respectively.

Bacterial isolates

The most prevalent bacteria from abscesses (Figure 1A) were *Streptococcus* (*Strep.*) *mitis* group ($n = 12$), *Strep. anginosus* group ($n = 7$), *Prevotella* (*P.*) *intermedia* ($n = 6$), *P. oralis* ($n = 5$), *P. denticola* ($n = 5$), *P. buccae* ($n = 5$), *P. oris* ($n = 3$), *Fusobacterium* (*F.*) *nucleatum* ($n = 3$) and other bacteria ($n = 14$). In patients with infiltrates (Figure 1B), the most common bacteria were *Strep. mitis* group ($n = 20$), *P. oralis* ($n = 8$), *P. intermedia* ($n = 6$), *Neisseria* (*N.*) spp. ($n = 6$), *Strep. sanguis* ($n = 6$), *Strep. pluranimalium* ($n = 3$), *Strep. salivarius* ($n = 3$), *F. nucleatum* ($n = 3$), *P. denticola* ($n = 3$), *P. buccae* ($n = 3$), *N. sicca* ($n = 3$) and other bacteria ($n = 20$).

Radiographical lesions

The median of the radiographical lesion area for all odontogenic processes was 9 mm^2 (the mean area was 12.9 mm^2; SD = 12.5, range = 0.4–46.2 mm^2). To carry out a median split, 'small lesions' were defined as ≤9 mm^2 ($n = 26$) and areas >9 mm^2 ($n = 25$) as 'large lesions'. The distribution of all bacteria at radiographically small (≤9 mm^2) and large (>9 mm^2) lesions is shown in Figures 1A (abscesses) and B (infiltrates), sorted by lesion extent.

Risk ratios for the bacterial distribution

In a further analysis, risk ratios for the distribution of each bacterial species at large vs small lesions in abscesses and infiltrates were calculated. An increased risk ratio (RR) to occur at large abscess lesions (Figure 2A) was observed for *P. oralis* (RR = 2.86), *P. buccae* (RR = 2.86), *Strep. anginosus* group (RR = 1.79), *P. oris* (RR = 1.43), *P. intermedia* (RR = 1.43) and *F. nucleatum* (RR = 1.43). In contrast, an increased risk ratio to occur at large infiltrate lesions (Figure 2B) was found for *Strep. salivarius* (RR = 2.94), *P. intermedia* (RR = 2.94), *N. sicca* (RR = 2.94), *P. buccae* (RR = 2.94), *Neisseria* spp. (RR = 1.47), *Strep. anginosus* group (RR = 1.47), *Capnocytophaga* spp. (RR = 1.47), *Prevotella* spp. (RR = 1.47), *P. melaninogenica* (RR = 1.47), *Strep. parasanguis* (RR = 1.47) and *Staphylococcus* (*Staph.*) *aureus* (RR = 1.47).

Susceptibilities of bacterial isolates

To identify the most effective antibiotics against the pathogenic bacteria in odontogenic abscesses and infiltrates, we compared the susceptibility rates of bacteria with an increased risk ratio in abscesses and infiltrates in this sub-population to the susceptibility rates of all bacteria isolated from abscesses and infiltrates, as described in our recent microbiological analysis [13].

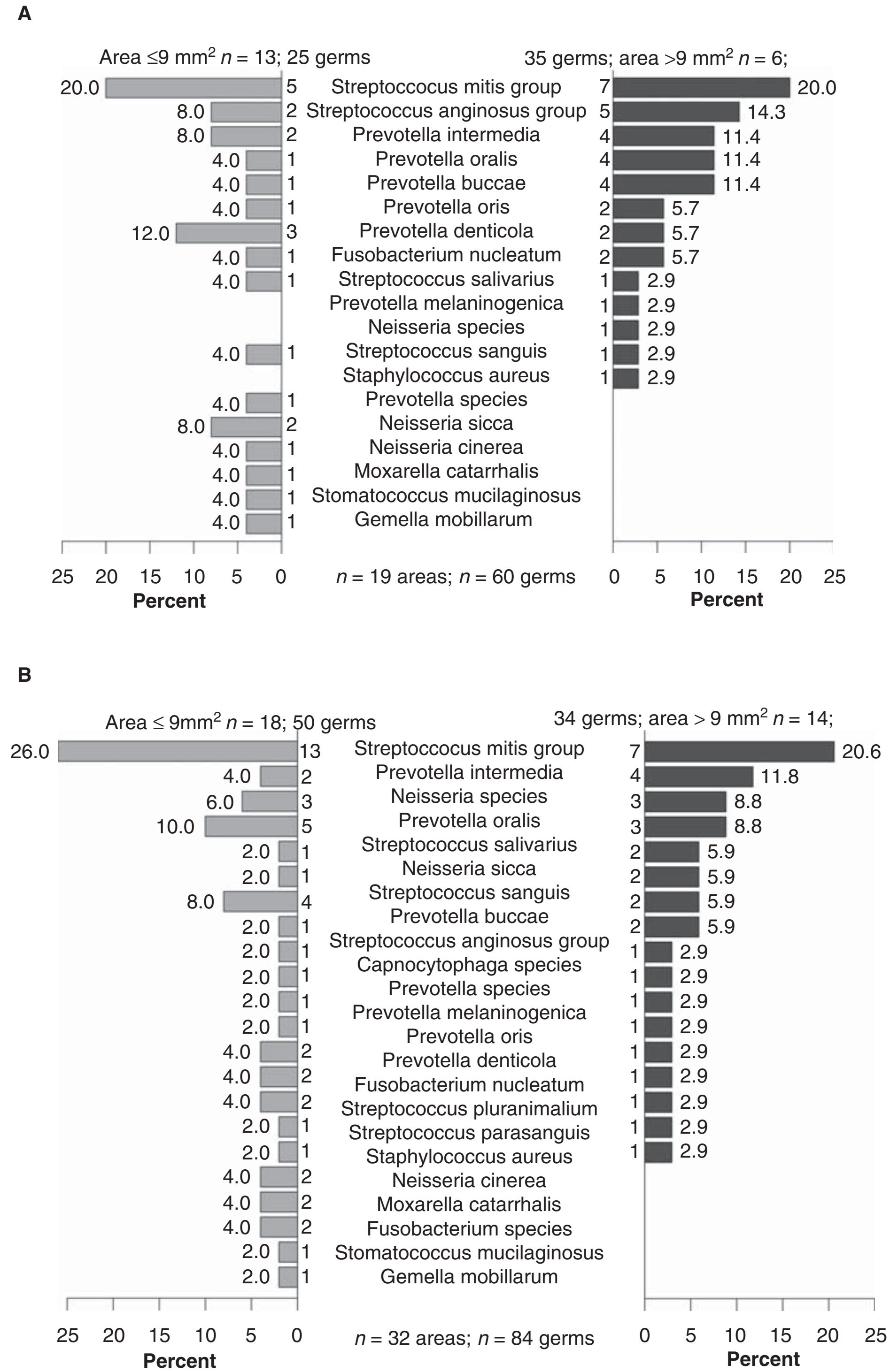

Figure 1. Distribution of bacteria at small (≤9 mm^2) and large (>9 mm^2) (A) abscess lesions and (B) infiltrate lesions.

In detail, the susceptibility rates of the risk-ratio-weighted bacteria were similar to the overall susceptibility rates in abscesses for MXF (98% vs 98%), LVX (87% vs 83%), PEN (73% vs 66%) and AMC (100% vs 97%) and in infiltrates for MXF (97% vs 98%), LVX (94% vs 86%), PEN (69% vs 67%), AMC (100% vs 96) and CLI (65% vs 60%) (Table I). The susceptibility rates of the risk-ratio-weighted bacteria from abscesses against CLI and DOX were considerably higher than the overall susceptibility rates of isolates from abscesses against CLI (79% vs 59%) and DOX (68% vs 51%). In patients with infiltrates only a moderate higher susceptibility rate could be observed for DOX of the risk-ratio-weighted bacteria compared to the overall susceptibility rate for DOX (62% vs 49%).

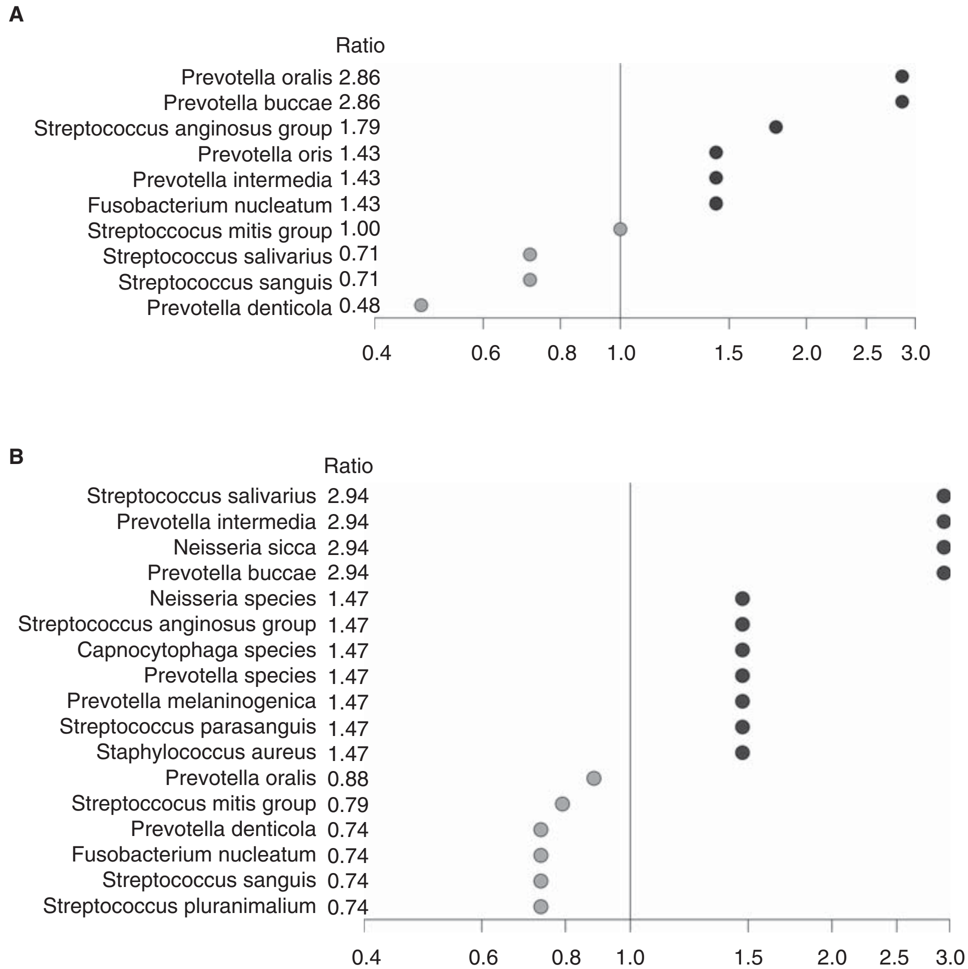

Figure 2. Risk ratio for (A) abscesses and (B) infiltrates, i.e. the risk of a species to occur on large vs on small lesions.

Discussion

To our knowledge, there are as yet no published data on a radiography-based score for the presumptive pathogenicity of odontogenic bacteria. Our study population originated from a prospective, randomized, double-blind, multi-center study comparing the efficacies and safety of MXF and CLI for the treatment of gingival inflammatory infiltrates and odontogenic abscesses ('MOCLI study') [12]. The microbiological analysis had shown that the *Strep. anginosus* group and hemolytic streptococci could be detected significantly more frequently in patients with abscesses than in patients with infiltrates. On the other

Table I. Susceptibility rates of bacteria with an increased risk ratio from abscesses and infiltrates compared to the susceptibility rates of all bacteria from abscesses and infiltrates.

	n	MXF	LVX	PEN	AMC	CLI	DOX
Abscesses							
Deduced susceptibility rates from present study*	62	98%	87%	73%	100%	79%	68%
MOCLI study+	95	98%	83%	66%	97%	59%	51%
Infiltrates							
Deduced susceptibility rates from present study*	71	97%	94%	69%	100%	65%	62%
MOCLI study+	110	98%	86%	67%	96%	60%	49%

*The susceptibility rates for bacteria with an increased risk ratio to occur at radiographically large abscesses [*P. oralis* ($n = 15$), *P. buccae* ($n = 8$), *Strep. anginosus* group ($n = 17$), *P. oris* ($n = 3$), *P. intermedia* ($n = 13$) and *F. nucleatum* ($n = 3$)] and infiltrates [*Strep. salivarius* ($n = 6$), *P. intermedia* ($n = 13$), *N. sicca* ($n = 5$), *P. buccae* ($n = 8$), *Neisseria* spp. ($n = 8$), *Strep. anginosus* group ($n = 17$), *Capnocytophaga* spp. ($n = 2$), *Prevotella* spp. ($n = 3$), *P. melaninogenica* ($n = 3$), *Strep. parasanguis* ($n = 3$) and *Staph. aureus* ($n = 3$)] were obtained from a recent microbiological analysis [13] and applied to all isolates of these bacterial species.
+For the purpose of comparison, the susceptibility rates for *all* bacteria from abscesses (overall 95 isolates) and from infiltrates (overall 110 isolates), obtained from the above cited analysis, are shown.

hand, viridans group streptococci and *Neisseria* spp. tended to occur more frequently in infiltrates than in abscesses. Ninety-eight per cent of all 205 isolates were susceptible to MXF, 96% to AMC, 85% to LVX, 67% to PEN, 60% to CLI and 50% to DOX [13].

A better understanding of the nature and the etiology of oral infections have led to improvements in the treatment [20]. The intention of our sub-group analysis of 51 patients of the above-mentioned study who received a radiologic assessment of the odontogenic lesions was to find a predictive score that could be indicative for infiltrate- or abscess-related pathogens. Due to the fact that observer's experience influences the performance in the interpretation of periapical lesions, three experienced examiners evaluated all radiographic images [21]. Interestingly, our sub-group analysis found the *P. oralis*, *P. buccae*, *P. oris*, *P. intermedia*, *F. nucleatum* and *Strep. anginosus* group to be bacteria with an increased risk ratio to occur at large abscess lesions, thereby clearly indicating that these pathogens are associated with odontogenic abscesses. On the other hand, an increased risk ratio to occur at large infiltrate lesions was found for *Strep. salivarius*, *Strep. parasanguis*, *Strep. anginosus* group, *N. sicca*, *Neisseria* spp., *P. intermedia*, *P. buccae*, *P. melaninogenica*, *Prevotella* spp., *Capnocytophaga* spp. and *Staph. aureus*, indicating that these bacteria are involved in the pathogenesis of odontogenic infiltrates. Moreover, our data suggest that the *P. buccae*, *P. intermedia* and *Strep. anginosus* group play a decisive role in the formation of both odontogenic abscesses and infiltrates.

Interestingly, our observation of *F. nucleatum* showing an increased risk ratio to occur in large odontogenic abscesses seems to be in agreement with an earlier study by Heimdahl et al. [22] in patients with orofacial odontogenic infections (treated with surgical drainage and antimicrobial therapy), with isolated *F. nucleatum*—and Gram-negative anaerobes in general—significantly more frequently from patients with severe infections. From this finding they concluded an association of this species with the severity of the infection.

Based on the radiological results in this sub-group and the observation of a specific spectrum of bacteria that was related to distinct odontogenic infections, we analyzed the weighted susceptibility rates of bacteria with an increased risk ratio from abscesses and infiltrates compared to the susceptibility rates of all bacteria from our above-mentioned study [13]. A comparison of both susceptibility rates is shown in Table I. MXF and AMC were found in the present sub-group study as well as in the multi-center MOCLI study to be the antibiotics with the highest susceptibility rates of 96–100% in both odontogenic infections. Similar susceptibility rates of the bacteria in the abscess group and the infiltrate group for LVX (83–94%) and PEN (66–73%) were demonstrated in the main MOCLI study as well as in the sub-group risk ratio study. Even though CLI tended to show moderately higher susceptibility rates in the abscess group of the risk ratio sub-group (79%) compared to the overall collective of the MOCLI study (59%), this antibiotic has been shown to be inferior to MXF in the clinical efficacy for the treatment of both odontogenic abscesses and infiltrates. If at all CLI should be provided for the therapy of odontogenic infections, our findings clearly indicate that it should be administered rather for odontogenic abscesses than for odontogenic infiltrates. Moreover, a geographically related pattern of the microbiota in samples might be considered in further research [23].

In conclusion, our radiography-based score indicates that certain *Prevotella* spp., *F. nucleatum*, and *Strep. anginosus* groups are involved in the pathogenesis of odontogenic abscesses and that various streptococci, *Neisseria* spp., *Capnocytophaga* spp., *Staph. aureus* and anaerobes as *Prevotella* spp. are relevant to the pathogenesis of odontogenic infiltrates. MXF has promising *in vitro* activity against odontogenic pathogens, which justifies its use for the treatment of odontogenic abscesses and inflammatory infiltrates.

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***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the performance and evaluation of the study protocol as well as for the content and writing of the paper.

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