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The epidemiological and clinical features of odontogenic infective endocarditis

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Ivana Šutej and Dragan Lepur were primarily responsible for data collection, the study conception and design. Material preparation and analysis were performed by Ivana Šutej, Vladimir Trkulja and Dragan Lepur. The first draft of the manuscript was written by Ivana Šutej, Kristina Peroš and Dragan Lepur, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Abstract

Purpose

Antibiotic prophylaxis (AP) of infective endocarditis (IE) in dental practice is a controversial topic. We evaluated the characteristics of the odontogenic IE, and assessed the practice and sources of information pertaining to the topic utilized by the Croatian dentists.

Methods

We conducted a retrospective review of consecutive medical charts of adult patients with IE, admitted to the University Hospital for Infectious Diseases in Zagreb, Croatia, between January 2007 and December 2017. In addition, a cross-sectional, self-reporting questionnaire survey was conducted with participation of 348 Croatian dentists.

Results

Of the 811 admissions for suspected IE (40.3% of all Croatian and 92.1% of all Zagreb hospitals), 386 patients were confirmed as definite IE: 68 with odontogenic IE and 318 with IE of other origin. Their first hospital admissions were analyzed. Definite odontogenic IE was defined as a positive echocardiographic result in conjunction with two separate positive blood cultures showing exclusive oral cavity pathogen or *Streptococcus viridans* associated with current or recent (<1 month) dental, periodontal, or oral cavity infection.

The annual number of new odontogenic IE patients appeared constant over time. In 91.2% of the cases, odontogenic IE was not preceded by a dental procedure; poor oral health was found in 51.5% of patients, and 47.1% had no cardiac condition that increases the IE risk. In-hospital mortality was 5.1% with conservative treatment and 4.5% with cardiac surgery and was much lower for odontogenic IE than in non-odontogenic IE (34.4%and14.6% , respectively). An increasing number of admissions for non-odontogenic IE was observed in parallel with an increasing number of staphylococcal IE. Surveyed dentists (500 invited, 69.6% responded) were aware of the AP recommendations, but were largely reluctant to treat patients at risk.

Conclusion

In people with poor oral health, AP should be considered regardless of cardiac risk factors. Improvement of oral health should be the cornerstone of odontogenic IE prevention.

Keywords: Infective Endocarditis; Odontogenic; Antibiotic; Prophylaxis

Introduction

Infective endocarditis (IE) is an uncommon disease with high morbidity and mortality. Despite improved diagnostic methods and available treatments, including cardiac surgery, the overall outcome remains unfavorable in substantial proportion of patients, even in high-income countries [1, 2]. IE is the fourth leading infectious cause of death worldwide, following pneumonia, sepsis and intra-abdominal abscesses [3]. Epidemiology of IE in developed countries has changed dramatically over the past two decades. Nowadays, it is mainly due to health care-associated infections, with *Staphylococcus aureus* as a leading causative agent, followed by *Enterococcus* (group D *Streptococcus*) and the *Streptococcus viridans* group (SVG). IE is typically seen in elderly patients and is associated with degenerative valvulopathies, prosthetic valves and cardiac implantable electronic devices, with more complex clinical features as compared to low-income countries [4].

The most recent guidelines advocate the use of AP only in high-risk patients before high-risk dental procedures [2, 5, 6]. Several epidemiological studies (USA, Canada, United Kingdom) yielded conflicting and inconclusive results about potential impact of guideline changes on the incidence of SVG IE, hence the AP still remains a controversial practice [7].

There are several important issues related to AP in dental medicine. Dentists are not always aware of the IE risk in their patients because of unavailable medical documentation, insufficient medical history or unclear communication with the patient's cardiologist. This results in inappropriate estimation of the patient's cardiac risk status. Moreover, dentists are commonly not sure which guidelines to follow and are not aware of the level of risk associated with a particular procedure, since risk-stratification criteria are typically not listed in the guidelines. Consequently, application of AP has been inconsistent and almost impossible to evaluate [8]. Also, primary care dentists frequently unnecessarily refer potential risk patients to secondary health care facilities out of (often unjustified) fear.

We explored the clinical and epidemiological characteristic of odontogenic IE over a 11-year period in Croatia (2007-2017) and attempted to assess the experience of Croatian dentists with the problem of IE prophylaxis.

Materials and methods

Study outline

A retrospective review of hospital records of all admissions due to suspected IE at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, Croatia, between January 1, 2007 and December 31, 2017, was undertaken in 2018 to assess clinical characteristics of odontogenic (oral/periodontal origin) IE. University Hospital for Infectious Diseases is a tertiary Zagreb University-affiliated hospital located in the City of Zagreb (the capital of Croatia). It is the leading national hospital of this kind which treats patients from all over Croatia. Its primary catchment area is the City of Zagreb and the surrounding region (Zagreb County) (a total of 1.107.623 residents; 880.636 of whom are ≥20 years of age). This represents ~25% of the total Croatian population (Croatian Bureau of Statistics; https://www.dzs.hr/Hrv/censuses/census2011/results/censustabsxls.htm; accessed April 20, 2019).

Routine health statistics data kept at the Croatian Institute of Public Health [records on discharge ICD codes (International Classification of Diseases) by institution] were consulted to approximate epidemiological trends over the time period covered by the study.

The second part of the study was a cross-sectional survey conducted during 2018. This survey aimed to assess experience, attitudes and adherence to guidelines of Croatian dentists, pertaining to antibiotic prophylaxis of IE in dental patients.

The study was approved by the Ethics Committees at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb (approval No. 01-397-2-2019) and School of Dental Medicine, University of Zagreb (approval No. 05-PA-30-IV-2/2019) and was conducted in line with the recommendations of the Declaration of Helsinki.

Eligible patients and outcomes of interest

The procedure for selection of patients for inclusion in the present study consisted of several steps (Figure 1): a) an initial identification of candidate patients was done by searching the electronic database maintained at the University Hospital for Infectious Diseases to identify all consecutive adults (≥18 years of age) hospitalized for a possible IE; b) after a re-check, hardcopy archival data were retrieved and reviewed by an infectious disease consultant subspecialized in intensive care (DL). Episodes/patients not meeting the modified Duke criteria [9] for IE were rejected, and definite IE episodes were further reviewed; c) since a number of patients were repeatedly hospitalized for IE during the observed period, only the first hospital admission episodes were included in the present study; d) finally, the selected patients were classified as odontogenic IE (IE of dental or periodontal origin) based on criteria shown in Table 1. Those who did not meet these criteria were classified as IE of "other origin". Those cases in which microbiological isolates confirmed *S. viridans* group pathogens, but which were not specifically identified, and in which the oral cavity origin of the causative agent was not confirmed, were considered as non-odontogenic (i.e., "IE of other origin").

Outcomes of interest were: the number of new patients with definite IE, odontogenic or "other", during the period under observation and by year; prevalence of causative agents overall and by IE type, also by year; comorbidities which represent a risk factor for IE, in particular known or newly diagnosed cardiac conditions (prosthetic valves, cardiovascular implantable electronic devices, valvular diseases); cardiac surgery treatment; mortality – in-hospital, during early postoperative period (for patients undergoing cardiac surgery), and overall. We also attempted to assess the extent to which the attending infectious disease specialists paid attention to the oral health status of IE patients (based on hospital records).

Survey among Croatian dentists

The first call for participation was sent to all dentists registered at the Croatian Dental Chamber through the members' mailing list. Since the response was poor, a second call was sent via a personalized e-mail message with instruction not to reply in case the questionnaire was filled out in the first call. In the second call, the invitation was sent to 500 dentists at targeted public health services (School of Dental Medicine University of Zagreb, Public Health Center, Department of Dental Medicine of the University Hospital Zagreb), and several private dentists' offices. The questionnaire was designed to collect information on attitudes related to treatment of IE risk patients, which sources of information and/or which professional guidelines are used, and general experience and knowledge about antibiotic prophylaxis for IE risk patients.

Data analysis

Because of the nature of data, no inferential statistical analysis was performed: the data was summarized using descriptive statistics. Considering the low number of newly diagnosed patients with dental/periodontal origin IE, data for the entire period under observation was summarized cumulatively. To illustrate trends over the observed period, three-year rolling averages were calculated for newly diagnosed patients with definite IE, and mortality and number of major infective causative agents were identified.

Results

A total of 811 hospital admission episodes due to suspected IE were identified at the University Hospital for Infectious Diseases (UHID) during the analyzed period. This represents 40.3% of hospital admissions for suspected IE in Croatia, and 92.1% of such admissions to all Zagreb hospitals (Zagreb region as a primary catchment area). Eventually, 548 episodes in 386 patients were verified as definite IE (Figure 1): 68 patients with IE of dental or periodontal origin (odontogenic IE) and 318 patients with IE of other origin. Their first admissions during the observed period were included in the present analysis. Repeated admissions were recorded almost exclusively for patients whose first episode was treated by cardiac surgery. The number of

readmissions was almost the same for both odontogenic and IE of other origin (on average 1.41 and 1.42 admissions per patient, respectively). The annual number of admitted odontogenic IE patients was consistently low during the analyzed period, while the number of patients with IE of other origin tended to increase between 2012 and 2017 (Supplementary Appendix, Figure S1-A). There were slightly more patients from other parts of Croatia than residents of the Zagreb region (Table 2). Demographics were similar between odontogenic IE and other IE patients, while high risk factors for the IE, such as cardiac implants and diabetes, were less common in the former (Table 2). Three features were of interest regarding odontogenic IE patients: First, in 62/68 (91.2%) of them, IE was *not* preceded (within the previous month) by any oral cavity infection or dental procedure. This suggests spontaneous bacteremia as a source of IE. Second, poor oral health status (advanced tooth decay, periodontal disease, residual roots) was found in 35/68 (51.5%) of the patients, but oral health status was not described at all in as many as 26 (38.2%) of odontogenic IE patients and only 7 (10.3%) were referred to a dentist or an oral surgeon. Finally, 47.1% of these patients had no cardiac condition known to increase the IE risk (Figure 2), 32.3% suffered from such a condition (but mostly moderate-risk conditions) that was known at admission (Figure 2), and in 20.6% patients such a condition was diagnosed during the index hospitalization (Figure 2). In one patient with a pre-existing known high-risk condition (prosthetic valve), IE occurred after a tooth extraction without antibiotic prophylaxis.

Staphylococci were by far most prevalent causative agents in other (non-odontogenic) IE, followed by enterococci and other bacteria, but *S. viridans* (undefined) was also identified (Table 3). The annual number of these major pathogen groups was generally constant over the observed period (Supplementary Appendix Figure S1-B), but with an increasing trend in the number of patients with staphylococci as causative agents that paralleled the increase in the number of admitted IE patients (Supplementary Appendix Figure S1-B). Cardiac structures affected by IE were similar in patients with odontogenic IE and IE of other origin (Table 2).

Of the 386 patients considered in the study, 49 were transferred from the UHID to other hospitals and their final treatment and outcome could not be tracked (Table 2). Of the 377 managed at the UHID (and collaborative institutions) until the disease was resolved or resulted in death, around 65% were treated only conservatively, and around 35% underwent cardiac surgery (Table 2). With either mode of treatment, in-hospital/perioperative mortality in odontogenic IE patients was similar and low (around 5%) (Table 2). In patients with IE of other origin, mortality was much higher, and considerably higher with only conservative vs. conservative *plus* surgical treatment (34.4% vs. 14.6%) (Table 2). No obvious mortality trend was observed over

the analyzed period (Supplementary Appendix Figure S1-C). In respect to particular causative microbiological agents, case fatality was by far the highest for staphylococcal infections (22.0%), followed by enterococcal infections (exclusively non-odontogenic IE patients) (Table 2).

Of the 500 invited dentists, 348 (response rate 69.6%) participated in the self-reporting survey. Most were employed in public practices (47.3%) or were affiliated with the School of Dental Medicine (13.5%) (also a part of the public health system), while 39.2% were private practitioners. General practice dentists (without a specialty) were the most represented group (70.6%), while oral surgeons were the most represented specialty (6.9%). The majority (86.8%) regularly inquire about their patients' medical condition, but only around 20% specifically ask about previous IE episode and conditions that increase IE risk. Most (54.0%) are reluctant to treat and some (9.8%) explicitly would not treat a patient at risk of IE. If applied, antibiotic prophylaxis is almost exclusively by amoxicillin or amoxicillin + clavulanate (94.5%). A 3.2% of the respondents never use antibiotic prophylaxis. Dentists' experience and sources of information pertaining to antibiotic prophylaxis of IE in dental patients are summarized in Supplementary Appendix Table S1.

Discussion

In contrast to some previous reports, in the present series (N=386) we found a relatively low proportion of infective endocarditis of dental/periodontal origin (odontogenic IE) (17.6%) [10, 11]. This is likely due to the strict(er) criteria we employed for identification of IE as odontogenic. Present observations suggest several conclusions. First, an IE associated with a dental procedure seems to be an extremely rare event: a link to a preceding dental procedure could be identified in only 6/68 (8.8%) of the patients with odontogenic IE (i.e., 1.5% of all IE patients). On the other hand, poor oral health status was found in a vast majority of these patients. Combined, these observations suggest spontaneous bacteremia of oral origin as the most important contributing factor in development of the odontogenic IE. It is therefore surprising and disappointing that a reasonably detailed inquiry about oral health by infectious disease specialist during the index hospitalization could reliably be identified in only around half of the patients (although, considering the nature of the present data, there is quite some uncertainty about this observation). In relation to the "oral cavity etiology" of IE, it should also be noted that a finding of *S. viridans* is commonly taken as an indicator of the odontogenic IE

etiology. Yet in the present series, oral cavity origin could be reliably established in only 12/27 (44.4%) patients with IE attributed to *S. viridans* [7]. Precautionary measures pertaining to the risk of IE associated with dental procedures/oral health are typically suggested for high-risk patients, i.e., those with cardiac implantable electronic devices, prosthetic valves or previous IE episodes [2, 5, 6]. Present observations suggest that odontogenic IE occurs in subjects with poor oral health irrespectively of the cardiac conditions that increase the IE risk: most (47.1%) of the verified odontogenic IE patients (N=68) had no contributing cardiac conditions and would be commonly considered as "low risk patients". Only 8 patients (7 with prosthetic valves, 1 with a previous IE) would be standardly considered as "high-risk patients". All other odontogenic IE patients (28/68, 41.1%) suffered from cardiac conditions that would standardly classify them as "moderate risk patients". It should be noted that, in around 1/5 (14/68) of odontogenic IE patients, such conditions were detected only during the index hospitalization for IE. Combined, these observations suggest that: a) all dental procedures, that are likely to result in bleeding and bacteremia (because of the type of procedure or poor oral health status), require antibiotic prophylaxis (AP). This pertains equally to high-risk patients (prosthetic valves, previous IE, cardiac implantable devices), and those not included in the current restricted guidelines. This means the AP should be applied also to patients classified as "moderate risk" of IE (e.g., those with mitral valve prolapse, bicuspid aortic valve), and even to "low risk patients", i.e., those with no known cardiac conditions [2, 5, 6]. Particularly, this refers to patients with a history of an undefined heart condition, cardiac murmur or rheumatic fever; b) poor oral health status *per se* seems to be a risk factor, irrespective of oral procedures/cardiac conditions.

Oral health in Croatia is poor - Croatia is ranked among the five European countries with the highest "Decayed, Missing, Filled Tooth" score (DMFT) [12]. Gradual improvement is expected among younger generations due to a national oral health program „Dentist passport", introduced in 2017 in elementary schools. In this respect, the observed low sensibility of infectious disease specialists to oral health is a problem that needs to be resolved. In 2005, a study was conducted in several Croatian hospitals to evaluate recommendations provided by cardiologists regarding management of patients with a high risk of IE undergoing oral surgery procedures [13]. A very high degree of variability was observed among the medical institutions and individual dentists. According to the published data and the present survey, Croatian dentists are well aware of the IE risk and the need for AP, but actual implementation of such measures is far from satisfactory [13]. Fear of treating high-risk patients is far too common, and divergence of AP recommendations

does not help. Also, the AP cannot substitute for public health measures and other actions aimed at improving oral health in the general population. During the period analyzed in the present study (2007-2017), recommendations on AP in dental patients have changed [7, 10, 14, 15]. The fact that we did not observe any particular trend, or a change in the annual number of admitted patients with odontogenic IE, indirectly suggests that these changes to the recommendations had no particular influence on occurrence of the odontogenic IE.

Short-term (in-hospital, perioperative) mortality in the current series of odontogenic IE patients was reasonably low (~5.0%), irrespectively of whether treatment was exclusively conservative or combined with cardiac surgery, and was considerably lower than in patients with IE of other origin. This is in line with other similar reports, and could be attributed (in part) to lower virulence of causative agents, resulting in fewer infectious (pyogenic) and non-infectious (e.g., immune-mediated, vascular, hemodynamic) complications [11]. In the present series, odontogenic IE patients also less commonly suffered from unfavorable conditions like diabetes mellitus and implantable cardiac devices than patients with IE of other origin. Considering the latter, we observed an increasing trend of admissions that was paralleled with an increasing trend of staphylococcal etiology - an observation in line with the reports from high-income countries [4, 16]. Two factors seem to have had relevant impact on in-hospital/perioperative mortality in these patients: staphylococcal IE and (early) cardiac surgery. Regarding surgery, it was not feasible to conduct a multivariate analysis that would reasonably control for confounding and allow for identification of an independent effect, but crude mortality rates suggest its importance: 14.6% with surgery vs. 34.4% without it. Several recent studies showing favorable outcomes after surgery in patients with IE indirectly support this observation [17-19]. In the present series, 34.8% of the non-odontogenic IE patients underwent surgery and several others with an indication did not, due to a high perioperative mortality risk (hemorrhagic stroke, refractory septic shock and end-stage liver disease). Such desperate conditions are particularly common among patients with staphylococcal IE [20, 21]. Considering the retrospective nature of the study, we could not reliably determine their percentage, but according to the published data, nearly 25% of patients with a surgical indication do not undergo surgery [20].

The present study has several limitations. Dentists participating in the questionnaire survey may not necessarily be representative of Croatian dentists. Invitations for participation were targeted and, although the response rate was rather high, all such surveys are subject to respondent bias. Single-center clinical data gathered through a retrospective chart review are subject to various biases arising from missing data, differences in

decision making between different attending physicians, errors and thoroughness in medical records keeping and similar reasons. The fact that case evaluation was performed by a single infectious disease specialist and not based on a consensus of several specialists could also be viewed as a limitation due to potential subjectivity. Conversely, we believed that uniform judgement of a single doctor, based on pre-defined clear-cut criteria would more successfully preclude classification errors. To reduce the risk of other potential biases, we included all consecutive IE admissions/patients and made no selection based on "data completeness". Rather, we restricted the data of interest to that which could be collected for all cases included. Consequently, we refrained from a multivariate analysis because we considered it impossible to achieve a reasonable control of confounding which would not result in a misleading inference. On the other hand, we consider the definition of odontogenic IE as used here to be the major strength of this study. It excludes misclassifications based solely on identification of *S. viridans* group (SVG) members as causative agents: SVG do not originate only from the oral cavity and should not be used as a synonym for odontogenic infections. In this respect, we would like to emphasize the need for active search for sources of bacteremia (e.g., colonoscopy, gastroscopy) in patients with non-odontogenic SVG infective endocarditis.

In conclusion, despite certain limitations, the present study seems to support the following conclusions: a) spontaneous odontogenic IE can occur regardless of the presence of cardiac conditions known to increase the IE risk; b) antibiotic IE prophylaxis should be applied in conjunction with dental procedures in all patients with "high risk" cardiac conditions (implantable devices, previous IE); c) in dental patients with poor oral health, AP should be applied also in patients with no cardiac conditions ("low IE risk") or with cardiac conditions standardly considered as "moderate risk of IE"; d) AP alone cannot reduce the risk of odontogenic IE – general improvement of oral health should be the cornerstone of such efforts; e) finally, there are no reasons for dentists to be reluctant to conduct dental procedures in "high-risk" patients - the procedures themselves are not the main contributing factor to odontogenic IE, particularly when appropriate AP is implemented.

Compliance with ethical standards

Funding: none

Conflict of interest: none declared

Ethical approval:

The study was approved by the Ethics Committees of the School of Dental Medicine, University of Zagreb, (approval No. 05-PA-30-IV-2/2019) and the University Hospital for Infectious Diseases "Dr Fran Mihaljević", Zagreb, Croatia (approval No. 01-397-2-2019). All procedures were conducted in accordance with the recommendations of the Declaration of Helsinki.

Informed consent: not applicable

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Tables

Table 1. Criteria for definite odontogenic infective endocarditis (IE).

Transthoracic/transesophageal echocardiography	Positive for IE according to Duke criteria [9]
Two separate positive blood cultures	Exclusive oral cavity pathogen or *Streptococcus viridans* associated with current or recent (<1 month) dental/periodontal/oral cavity infection

Table 2. Demographic and clinical characteristics of patients with definite infective endocarditis (IE) (first hospital admission) hospitalized at the University Hospital for Infectious Diseases (UHID, Zagreb, Croatia) between January 1, 2007 and December 31, 2017 – overall and by origin of endocarditis.

	All patients	**Dental/periodontal origin IE**	**Other origin IE**
N	386	68	318
Zagreb residents	161 (41.7%)	31 (45.6%)	130 (40.9%)
Patients from other parts of Croatia	225 (58.3%)	37 (54.4%)	188 (59.1%)
Men	262 (67.9%)	48 (70.6%)	214 (67.3%)
Age	63 (48-73)	60 (43-69)	63 (49-74)
Intravenous drug user	13 (3.3%)	1 (1.5%)	12 (3.8%)
Prosthetic valve/implantable electronic device	81 (20.9%)	7 (10.3%)	74 (23.2%)
Diabetes mellitus	66 (17.0%)	6 (8.8%)	60 (18.8%)
Cardiac structures affected by IE			
Aortic valve	176 (45.6%)	36 (52.9%)	140 (44.0%)
Mitral valve	151 (39.1%)	27 (39.7%)	124 (38.9%)
Tricuspid valve	26 (6.7%)	0	26 (8.1%)
Aortic and mitral valve	20 (5.2%)	5 (7.3%)	15 (4.7%)
Pacemaker lead	8 (2.0%)	0	8 (2.5%)
Mitral and tricuspid valve	4 (1.0%)	0	4 (1.2%)
Pulmonary valve	1 (0.2%)	0	1 (0.3%)
Transferred alive – outcome unknown*	49 (12.7%)	7 (10.3%)	42 (13.2%)
Managed at UHID + collaborative institutions	337	61	276
Exclusively conservative treatment (UHID)	219 (65.0%)	39 (63.9%)	180 (65.2%)
Cardiac surgery (collaborating institutions)	118 (35.0%)	22 (36.1%)	96 (34.8%)
In-hospital mortality: conservative treatment	64/219 (29.2%)	2/39 (5.1%)	62/180 (34.4%)
Perioperative mortality: cardiac surgery	15/118 (12.7%)	1/22 (4.5%)	14/96 (14.6%)
Overall mortality in UHID-managed patients	79 (23.4 %)	3 (4.9%)	76 (27.5%)
Case fatality by major causative agent group			
Staphylococci	41/186 (22.0%)	---	---
Enterococci	9/56 (16.0%)	---	---
S.viridans (undefined)	1/27 (3.7%)	---	---

Data are median (1^{st}-3^{rd} quartile) or count (percent)

* Patients were diagnosed and started treatment at UHID, but were transferred to other hospitals while IE was still not resolved. Their further treatment and outcomes could not be tracked.

Table 3. Microbiological causative agents identified in patients with definite infective endocarditis (IE) (first hospital admission) hospitalized at the University Hospital for Infectious Diseases (UHID, Zagreb, Croatia) between January 1, 2007 and December 31, 2017 – overall and by origin of endocarditis.

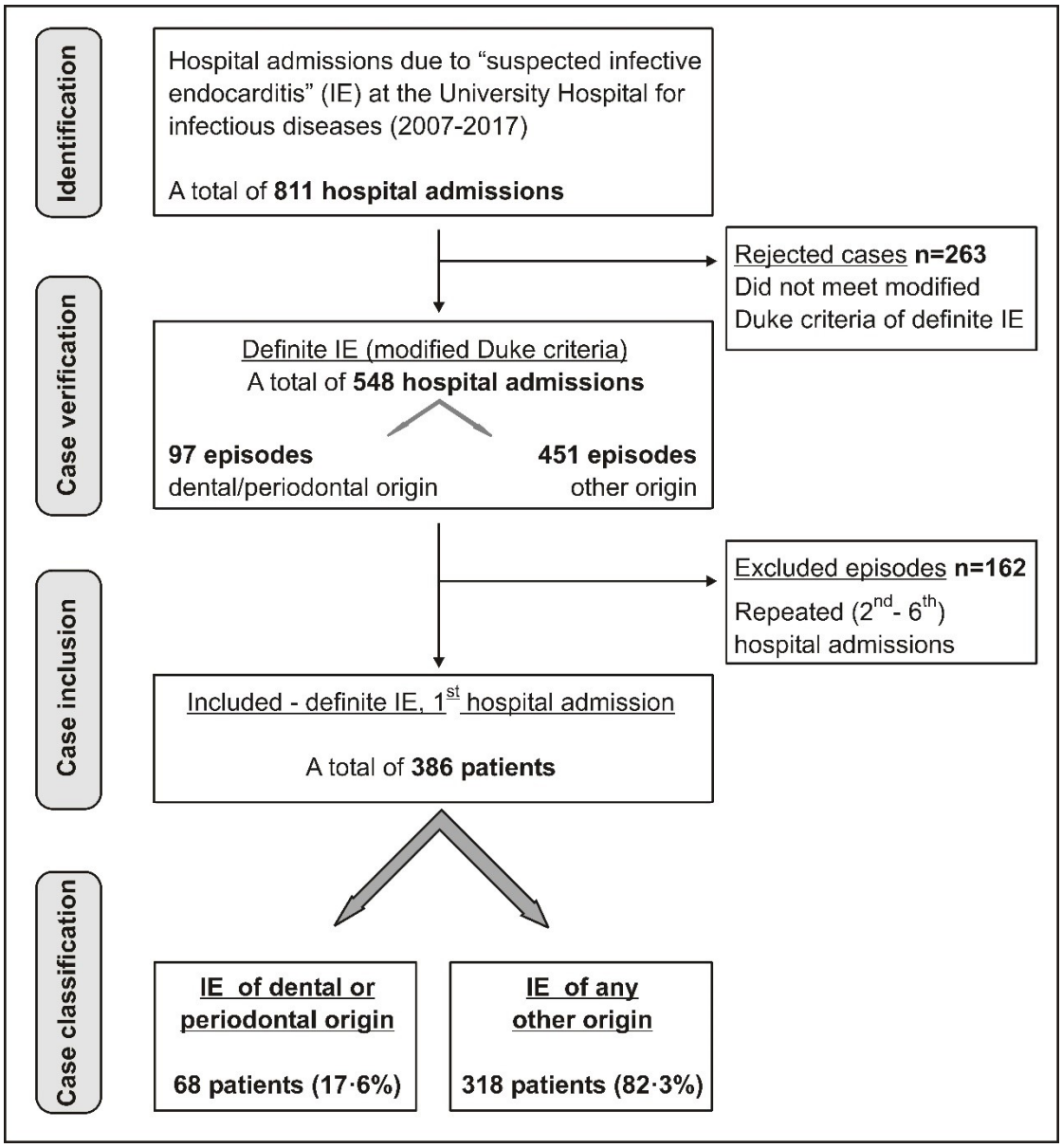
	All patients	**Dental/periodontal origin IE**	**Other origin IE**
N	386	68	318
Staphylococci overall	**186**	**NA**	**186**
Methicillin-sensitive *S. aureus*	133	NA	133
Methicillin-resistant *S. aureus*	17	NA	17
Coagulase-negative staphylococci	15	NA	15
Other staphylococci	21	NA	21
Oral pathogens overall	**83**	**68**	**15**
***S.viridans* (undefined)**	**27**	**12**	**15**
S.mitis	16	16	0
S. sanguinis	8	8	0
S.oralis	4	4	0
Gemella morbillorum	4	4	0
S.gordonii	4	4	0
S.mutans	4	4	0
S.constellatus	3	3	0
Abiotrophia defectiva	2	2	0
Aggregatibacter aphrophilus	2	2	0
S.anginosus	2	2	0
S.salivarius	2	2	0
Other	5	5	0
Enterococci overall	**56**	**NA**	**56**
Enterococcus faecalis	55	NA	55
Enterococcus faecium	1	NA	1
Other bacteria	**61**	**NA**	**61**

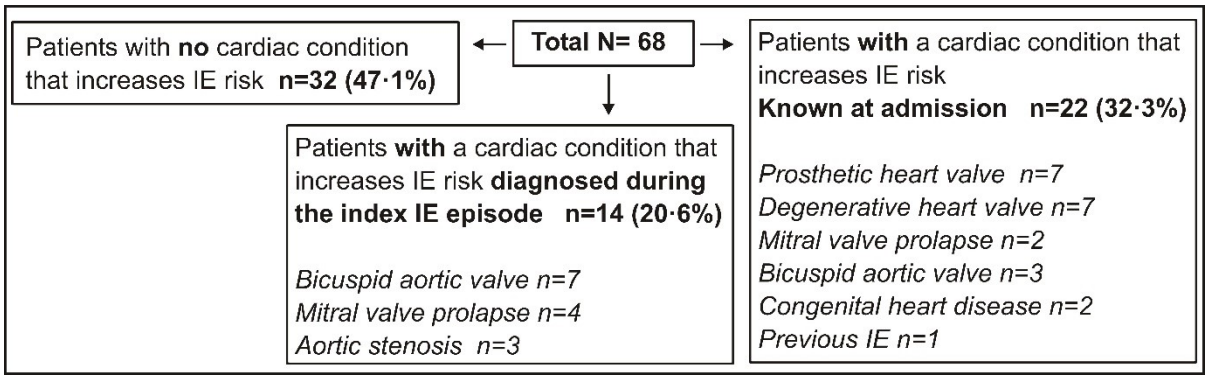
Data are counts
NA- not applicable

Figure legends

Figure 1. Selection of patients included in the present analysis. In the first step (identification), all records pertaining to hospital admissions due to "suspected infective endocarditis" between January 1, 2007 and December 31, 2017 at the University Hospital for Infectious Diseases (Zagreb, Croatia) were retrieved. In the next step (case verification), only episodes meeting the modified Duke criteria [9] for definite IE were kept. Some patients were repeatedly hospitalized during the observed period, but only the first episodes were included (case inclusion) in the present analysis. Finally, patients were stratified in respect to the IE origin – as those with IE of dental or periodontal origin and those with IE of any other origin.

Figure 2. Breakdown of patients with infective endocarditis (IE) of dental/periodontal origin in respect to presence of cardiac conditions that increase the IE risk (known at admission, or previously unknown and detected during the index hospitalization).


Identification
Hospital admissions due to "suspected infective endocarditis" (IE) at the University Hospital for infectious diseases (2007-2017)
A total of 811 hospital admissions
Rejected cases n=263
Did not meet modified Duke criteria of definite IE
Case verification
Definite IE (modified Duke criteria)
A total of 548 hospital admissions
97 episodes
dental/periodontal origin
451 episodes
other origin
Case inclusion
Excluded episodes n=162
Repeated (2nd- 6th) hospital admissions
Included - definite IE, 1st hospital admission
A total of 386 patients
Case classification
IE of dental or periodontal origin
68 patients (17·6%)
IE of any other origin
318 patients (82·3%)


Patients with **no** cardiac condition that increases IE risk **n=32 (47·1%)**
Total N= 68
Patients **with** a cardiac condition that increases IE risk **diagnosed during the index IE episode n=14 (20·6%)**
Bicuspid aortic valve n=7
Mitral valve prolapse n=4
Aortic stenosis n=3
Patients **with** a cardiac condition that increases IE risk
Known at admission n=22 (32·3%)
Prosthetic heart valve n=7
Degenerative heart valve n=7
Mitral valve prolapse n=2
Bicuspid aortic valve n=3
Congenital heart disease n=2
Previous IE n=1

The epidemiological and clinical features of odontogenic infective endocarditis

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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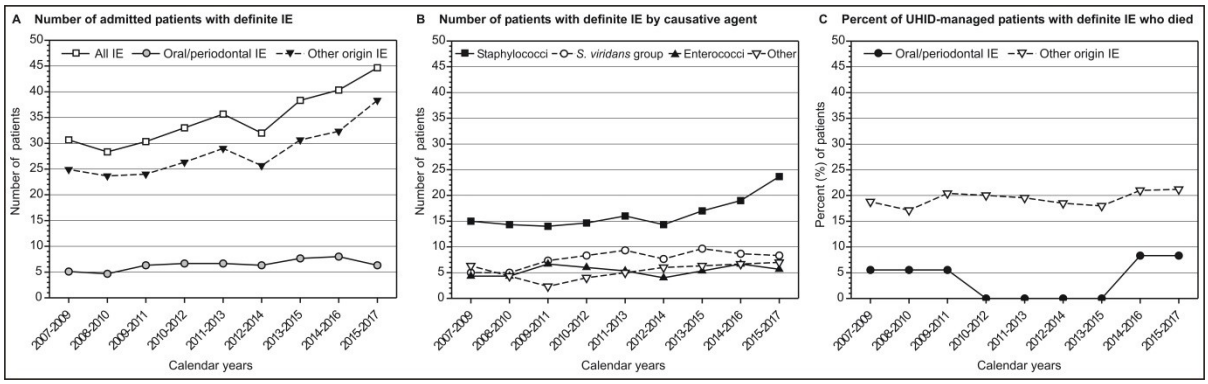

Figure S1. Trends [illustrated by 3-year rolling averages (symbols)] regarding the number of patients with definite infective endocarditis (IE), their mortality and causative agents observed between January 1, 2007 and December 31, 2017, at the University Hospital for Infectious Diseases (UHID) (Zagreb, Croatia). **A**. Number of patients with definite IE (overall and by IE origin) (only first hospitalizations for a particular patient during the observed period). **B**. Number of patients with definite IE in respect to microbiological causative agents – major groups. **C**. Percentage of patients with definite IE, managed at UHID and collaborative institutions who died during the index hospitalization. Excluded were 49 out of 386 patients who were admitted and diagnosed at UHID, but were transferred to other institutions while the treatment was in progress – their further treatment and outcomes could not be tracked.

Table S1. Extract from the questionnaire survey conducted among 500 targeted Croatian DMDs (348 or 69.6% responded) to illustrate their experience with patients at high risk of infective endocarditis (IE) and their sources of information about recommendations regarding antibiotic prophylaxis in dental patients.

Question	**N (%)**
Have you ever treated a patient at risk for IE over the last 10 years in your dental practice?	
No	57 (16.4)
Yes	291 (84.6)
I usually check the guidelines on IE antibiotic prophylaxis in dentistry from the following source:	
American Heart Association (AHA)	87(25.0)
The National Institute for Health and Care Excellence (NICE)	4 (1.1)
European Society of Cardiology (ESC)	17 (4.9)
Croatian Cardiac Society	46 (13.2)
One of the Croatian national healthcare webpages	32 (9.2)
Colleagues that I trust	66 (19.0)
Pubmed	22 (6.3)
Other	64 (21.3)