Antibiotic Prescription Patterns in Ambulatory Dental Care in Kosovo

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Abstract

Background: Globally, the level of antibiotic prescription in dental care is increasing annually, and evidence indicates a high level of antibiotic misuse. This survey evaluated the prescription of antibiotics in primary dental care of health system of Kosova. Methods: Antibiotic use data for 1825 registered patients over a 1-year period were randomly collected and analyzed. These data are presented as the Defined Daily Dose [DDD]/1,000 inhabitants/day. Results: The prescription rate of antibiotics for all registered patients was 7.9%. The total use of antibiotics in dental primary care was 2.17 DDD/1,000 inhabitants/day. A total of 6 individual antibiotics were identified in this survey. The most frequently used antibiotic was co-amoxiclav (J01CR02), with a 1.16 DDD, followed by amoxicillin (J01CA04), with a 0.78 DDD. Other individual antibiotics that were used significantly less frequently included ceftriaxone (J01DD04), with a 0.11 DDD, cefalexin (J01DB01), with a 0.09 DDD, procaine benzyl penicillin (J01CE09), with a 0.02 DDD, and gentamicin (J01GB03), with a 0.01 DDD. Conclusion: The results of this survey indicate that a high prescription rate is not rational in primary dental care in Kosovo. The prescription of antibiotics in Kosovo is exclusively empiric without prior sensitivity testing, which may negatively impact bacterial resistance profiles. The use of broad-spectrum antibiotics should be replaced with that of more narrow-spectrum antibiotics, and more restrictive prescription patterns should be applied. For qualitative improvement in the prescription of drugs in these groups, we recommend the implementation of a restrictive antibiotic policy.

Key Words: Antibiotic use, Dentistry

Introduction

Antibiotics represent one of the most important drug groups in clinical practice, considering their role in the control of infectious diseases and their impact on public health. Dental care service includes different types of care, such as the treatment of odontogenic infections. Globally, the level of antibiotic prescription in dental care is increasing annually, and antibiotics are used extensively in the field of endodontics [1,2]. These prescription habits reflect the trends of overuse and misuse of antibiotics in dental practice. The extensive utilization of antibiotics in clinical practice has been determined to be a leading factor for the emergence of antibiotic resistance [3]. However, the relationship between the antibiotic prescription rate and bacterial resistance is relatively complex. Evidence indicates that antibiotic use influences resistance, but a persuasive, quantitative relationship between the volume of antibiotic use and bacterial resistance has not yet been established [4]. Antibiotic prescription by dental practitioners has an important impact on the rate of general antibiotic prescription use, and an attempt has been made to establish a surveillance system for the monitoring and control of the use of these drugs [5,6].

The rational and effective prescription of antimicrobials is imperative in dental practice, and it is necessary to implement an antimicrobial prescription monitoring system and antibiotic stewardship program. One important strategy for reaching the objective of rational antibiotic prescription is the implementation of drug utilization studies, as defined by the World Health Organization (WHO) [7]. Antibiotic utilization studies enable analyses of antibiotic use, provide feedback data on the distribution of prescriptions and measure the effects of restrictive measures on the level of antibiotic use [8,9]. Hence, such studies are considered a fundamental starting point in establishing an effective antibiotic stewardship program, with the main objectives of improving the treatment efficacy and decreasing bacterial resistance; this program can also be used as a pharmaco-epidemiological measure for implementation of a national restrictive antibiotic policy [10]. Systematic reviews of antibiotic use have revealed effective measures by integrating the results of studies demonstrating effective restrictive programs and decreased antibiotic use [11]. Despite the systematic monitoring and extensive antibiotic use programs in developed countries, the data on antibiotic use in most low- and middle-income countries are scarce and insufficient. Specifically, information on antibiotic use in dental practice is widely unavailable. Thus, the use of an antimicrobial prescription monitoring system and antibiotic stewardship program will enable the reduction of prescription errors, increase the safety of drugs and reduce the triggering of drug resistance.

Therefore, our survey was conducted to determine the antibiotic prescription pattern in primary dental care in Kosovo, to analyze prescription habits, to identify eventual misuses of antibiotics and to facilitate the formulation of standards for the rational prescription of these drugs.

Material and Methods

Ethics statement

This survey was performed according to the guidelines of the World Medical Association Declaration of Helsinki using an anonymous system of patient data collection. According to the local regulations in Kosovo, health workers who use descriptive surveys may collect data using an anonymous system with committee approval.

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Methodology

This study was conducted in the six administrative regions of primary dental health care in Kosovo. In each region, the dental services of the Main Family Medicine Center (MFMC) and of one other Family Medicine Center (FMC) were included in the survey. In total, the study was conducted in twelve (12) primary dental care centers in Kosovo.

In this retrospective study, 27375 patient records were analyzed, and from them, one record was randomly selected out of every fifteen records, for a total of 1825 patient records. We used the dental patient register from the beginning of January to the end of December 2015.

Data were collected manually by our team using an approved protocol for data collection. The members of the collection team attended training on drug utilization.

The indicators specified by the WHO Action Programme on Essential Drugs and the International Network for the Rational Use of Antibiotics were included on the data collection form [12].

The Anatomical Therapeutic Chemical (ATC) Classification System of WHO was applied in this study. The WHO recommends the use of the Drug Utilization Research (DUR) methodology, which includes the Anatomic Therapeutic Classification/Defined Daily Dose (ATC/DDD) index [13].

The ATC/DDD index ATC codes and DDD values for each individual drug registered. We included all antibacterials for systemic use (ATC J01), excluding those used as intestinal anti-infectives (ATC A07AA).

The patient records were assigned a code for identification, and the patient data were collected using an anonymous methodology and entered into an approved excel spreadsheet These data included patient age and sex, the diagnosis according to the International Statistical Classification of Diseases and Related Health Problems: 10th Revision (ICD-10) code, the daily dose of the antimicrobial drug used, the antimicrobial classification by ATC codes, the trade or generic name of the drug, the number of antibiotics prescribed to each patient and the antibiotic administration route.

In this study, the data were analyzed using Microsoft® Excel software 2007, USA. The results are presented using descriptive statistics, such as the frequency of distribution. Quantitative analysis was performed using a methodology based on DDD/1,000 inhabitants/day and ATC, according to the WHO [14].

Results

A total of 1825 patients were included in our survey. Among them, 49.3% were male, and 50.7% were female. The gender distributions did not significantly differ across the six regions (regions 01 to 06).

The prescription rate of antibiotics for the total registered patients was 7.9%. The percentages of patients treated with antibiotics varied across the regions, ranging from a low of 4.75% in region 01 to a high of 12.8% in region 02; in addition, the rates were 10.5% and 9.2% in regions 04 and 03, respectively. Of the 1825 patients, 87 (4.8%) underwent surgical interventions, whereas the other 1738 received pharmacological dental treatment (*Table 1*).

For the 144 patients who were prescribed antibiotics, 152 antibiotic prescriptions were registered. Comprehensive analyses of antibiotic use revealed that 136 patients were prescribed only 1 antibiotic, whereas 8 received a combination of 2 antibiotics. Of the 8 patients who received 2 antibiotics, 7 received the combination ceftriaxone and gentamicin, and 1 was prescribed the combination of procaine, benzyl penicillin and gentamicin.

Table 1. General data and quantitative indicators of antibiotic prescribing.

Region	Nr. patient	Nr. Male (Nr./%)	Nr. Female (Nr./%)	Nr. Patients W/ antibiotic (%)	Nr. Patients W/0 antibiotic (%)	Nr. Patients with surgical interventions (%)	Nr.Patients with nonsurgical interventions (%)
01 (Prishtina)	362	169 (46.7%)	193 (53.3%)	17 (4.75%)	345 (95.3%)	17 (4.7%)	345 (95.3%)
02 (Mitrovica)	288	145 (50.3%)	143 (49.7%)	37 (12.8%)	251 (87.2%)	8 (2.8%)	280 (97.2%)
03 (Peja)	303	156 (51.5%)	147 (48.5%)	28 (9.2%)	275 (90.8%)	7 (2.3%)	296 (97.7%)
04 (Prizren)	306	154 (50.3%)	152 (49.7%)	32 (10.5%)	274 (89.5%)	31 (10.1%)	275 (89.9%)
05 (Ferizaj)	266	129 (48.5%)	137 (51.5%)	14 (5.3%)	252 (94.7%)	12 (4.5%)	254 (95.5%)
06 (Gjilan)	300	146 (48.7%)	154 (51.3%)	16 (5.3%)	284 (94.7%)	12 (4.0%)	288 (96%)
Total	1825	899 (49.3%)	926 (50.7%)	144 (7.9%)	1681 (92.1%)	87 (4.8%)	1738 (95.2%)

The antibiotic prescription rate was slightly higher for the male patients than for the female patients (52% vs. 48%, respectively). In addition, greater differences in this rate between genders were detected among the different regions. Specifically, in regions 01 and 02, more males than females used antibiotics (64.7% and 58.1%, respectively), whereas in regions 03 and 04, more females than males used them (56.7% and 53.1%, respectively).

Analysis of the prescription of antibiotics by generic name and brand name revealed that generic antibiotics were prescribed significantly more frequently than brand name antibiotics (74.3% vs. 25.7%, respectively). Specifically, in regions 02 and 03, generic antibiotics were prescribed at significantly higher rates of 97.7% and 96.7%, respectively, compared with brand name antibiotics, whereas the opposite

was observed in region 04, where the prescription rate of brand name antibiotics was 62.5%.

The total percentage of oral antibiotics was significantly higher than that of parenteral antibiotics (78.3% vs. 21.7%, respectively). Absolute prescription rates (100%) for oral antibiotics were registered in regions 01, 05 and 06, whereas in region 02, the rate for parenteral antibiotics was higher than that for oral antibiotics (51.2% vs. 48.8%, respectively) (*Table 2*).

Table 2. *Qualitative indicators of antibiotic prescribing.*

Region	Nr.antibiotics	Male (Nr./%)	Female (Nr./%)	Generic name	Brand name	Oralantibiotics	Parenteral
(Nr./%)	(Nr./%)	(Nr./%)	antibiotics (Nr./%)				
01 (Prishtina)	17	11 (64.7%)	6 (35.3%)	6 (35.3%)	11 (64.7%)	17 (100%)	0 (0%)
02 (Mitrovica)	43	25 (58.l%)	18 (41.9%)	42 (97.7%)	1 (2.30%)	21 (48.8%)	22 (51.2%)
03 (Peja)	30	13 (43.3%)	17 (56.70%)	29 (96.7%)	1 (3.3%)	27 (90.0%)	3 (10%)
04 (Prizren)	32	15 (46.9%)	17 (53.1%)	12 (37.5%)	20 (62.50%)	24 (75%)	8 (25%)
05 (Ferizaj)	14	7 (50.0%)	7 (50.0%)	10 (71.4%)	4 (28.6%)	14 (100%)	0 (0%)
06 (Gjilan)	16	8 (50.0%)	8 (50.0%)	14 (87.5%)	2 (12.50%)	16 (100%)	0 (0%)
Total	152	79 (52.0%)	73 (48.0%)	113 (74.3%)	39 (25.7%)	119 (78.3%)	33 (21.7%)

Analyses of medical records did not indicate that antibiotic sensitivity testing was conducted for any patient. Therefore, we considered that the prescription of antibiotics was performed empirically.

Figure 1 depicts the percentage of utilization for each antibiotic group, presented as DDD/1000 inhabitants/day (DID). The distribution shows that beta-lactam antibiotics (J01C) were the most frequently used, with a 1.95 DID, whereas other beta lactams (J01D) and aminoglycosides (J01G) were used significantly less frequently (with 0.2 and 0.01 DDDs, respectively).

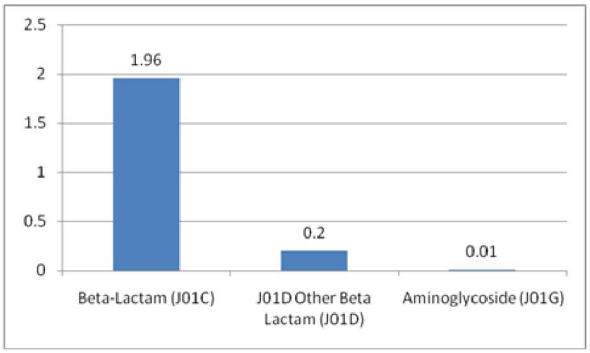

Figure 1. *Percentage of antibiotic drug uses DDD/1000 inhabitants per day.*

Figure 2 shows the DID values for the six antibiotics assessed in this survey. The results showed that dentists in primary dental health care in Kosovo prescribed only six individual antibiotics. The most frequently used antibiotic was co-amoxiclav (J01CR02), with a 1.16 DID, following by amoxicillin (J01CA04), with a 0.78 DID. Other antibiotics that were used significantly less frequently included ceftriaxone (J01DD04), with a 0.11 DID, cefalexin (J01DB01), with a 0.09 DID, procaine benzyl penicillin (J01CE09), with a 0.02 DDD, and gentamicin (J01GB03), with a 0.01 DID.

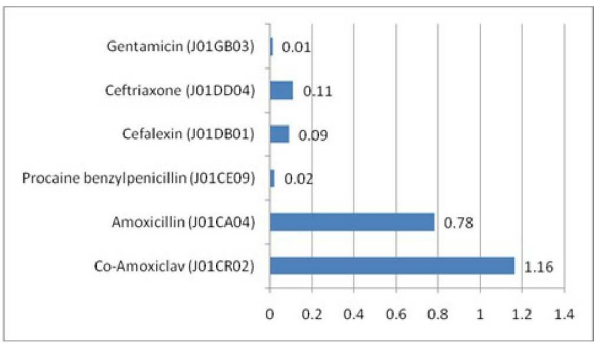

Figure 2. *Percentage of individual drug uses DDD/1000 inhabitants per day.*

Overall, 10 classes of diagnosis were recorded for all patients registered in our survey database. The class of diagnosis K08 (Other diseases of teeth and supportive structures) was the most common at 41.2%, followed by class K04 (Other diseases of hard tissue of teeth) at 37.6% and K02 (Dental caries) at 10.8%. Other classes of diagnosis, such as K05 (Gingivitis and periodontal diseases), K00 (Disorders of tooth development and eruption), and K10 (Other jaw diseases), were documented less frequently (*Figure 3*).

During our survey, six classes of diagnosis were recorded for which antibiotics were prescribed (*Figure 4*). The predominant class was K08 (Other diseases of teeth and supportive structures) at 62.5%, followed by K04 (Diseases of pulp and periapical tissues) at 28.5%. Other classes were detected at smaller percentages, including K05 at 2.1%, A31 (Infection due to another mycobacteria) at 1.3%, K10 (Other jaw diseases) and S10 (Superficial injuries of teeth).

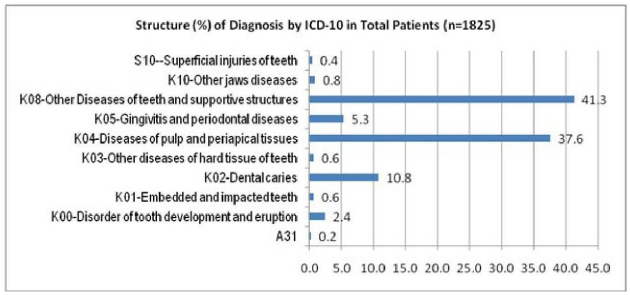

Figure 3. *Percentage of diagnosis by ICD-10 in total patients (n=1825).*

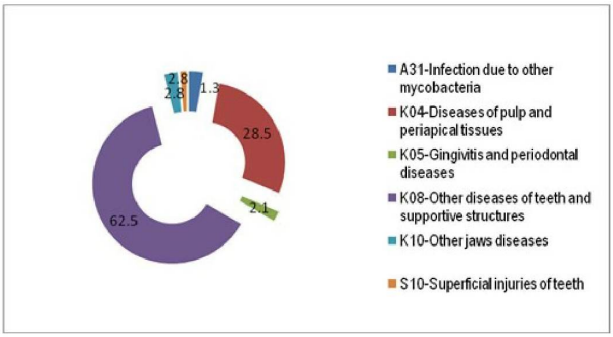

Figure 4. *Percentage of diagnosis by ICD-10 in total patients with antibiotics (n=144).*

Discussion

The surveillance of antibiotic use in primary dental care in Kosovo was a complex and time-consuming process because the data were manually collected from patient records. As some medical records were not well documented, it was necessary to obtain additional clarification by directly contacting the dentists.

This is the first comprehensive antibiotic surveillance study conducted to assess primary dental care in Kosovo using the WHO methodology for antibiotic use, which is a drug utilization research methodology based on the Anatomic Therapeutic Classification/Defined Daily Dose (ATC/DDD) index [15]. The rate of antibiotic use for the total dental patients was 7.9%, which can be considered optimal under the circumstances of this study because applicable antibiotic treatment guidelines and protocols are not available in Kosovo; thus, there are no restrictions on antibiotic prescription in primary dental care [16]. Total outpatient antibiotic (ATC group J01) use was 2.17 DID. In addition, beta-lactam antibiotics (J01C) were the most frequently used. These antibiotics can be considered a rational choice for use in dental practice. The total use of this antibiotic group is significantly higher is significantly higher compared with those reported by other international surveys conducted in dental practices [17].

Analysis of the different groups of antibiotics revealed that only 3 groups were prescribed, which indicates that the choice of antibiotics by dentists is relatively rational, homogenous and consensual. Further, the evidence obtained from analysis of the prescription rates of the antibiotic groups does not support the prescription of other beta-lactam antibiotics, especially aminoglycosides, without prior antibiotic sensitivity testing [18].

A total of 6 individual antibiotics were recorded in the survey, which is a relatively small number and is attributed to the lack of protocols for the treatment of dental infections in primary dental care. The results of the surveys showed that co-amoxiclav, a broad-spectrum antibiotic, was the most frequently prescribed drug (with a 1.16 DID) in all regions of Kosovo, and it appears to be the first-line antibiotic for use in the treatment of dental infections. This antibiotic was selected empirically, as the bacterial resistance rate for dental infections in Kosovo was unknown. The rate of prescription of co-amoxiclav was high, in contrast with its prescription rates in developed countries. Moreover, Kuriyama et al. have indicated that there are no differences in the clinical outcomes of patients using penicillin V, amoxicillin, or the combination of amoxicillin and clavulanate [19].

The second most commonly used antibiotic was amoxicillin, which is considered one of safest empirical antibiotics. It has an appropriate spectrum of activity for oral bacteria and can reach an effective gingival concentration at the site of action [20]. Co-amoxiclav (53.5%) and amoxicillin (35.9%) were the most frequently used antibiotics with a combined prescription rate of 89.4% whereas the combined prescription rate for the other 4 antibiotics was only 10.6% of all prescriptions. Ceftriaxone (J01DD04) was the third most frequently used antibiotic, with a 0.11 DID (5.4% of the total prescribed antibiotics). Because ceftriaxone is a parenteral, third-generation cephalosporin, its use in primary dental care is not considered rational and is not supported by clinical evidence. This antibiotic is prescribed for the treatment of dental abscess, and its use in primary dental care could trigger bacterial resistance [21].

Cephalexin was the fourth most commonly used antibiotic, with a 0.09 DID (4.1%), and it is the antibiotic of choice for some dental infections due to its good bone penetration [18].

The use of gentamicin (with a 0.01 DID and 0.5% prescription rate) is considered less rational due to clinical evidence indicating that it should be reserved for the treatment of select Gram-negative infections, usually occurring in hospital settings [22,23].

During our survey, 10 classes of diagnosis were identified among the total patients according to the International Classification of Diseases (ICD 10). The most common classes of diagnosis were K08 (Other disease of teeth and supportive structures) at 41.2%, K04 (Other diseases of hard tissue of teeth) at 37.6%, and K02 (Dental caries) at 10.8%. The most frequent classes of diagnosis for the patients taking antibiotics were very similar to those for all registered patients. For the group of patients who received antibiotics, the predominant class of diagnosis was K08 (Other disease of teeth and supportive structures) at 62.5%, followed by K04 (Diseases of pulp and periapical tissues) at 28.5%.

A limitation of the present study is that the data were manually collected from the patients' medical records. In

general, based on our main findings, we recommend improving the system used for data recording, management and maintenance, which may result in a better and more efficient drug prescription monitoring system in primary dental care. Additionally, we recommend the development of treatment guidelines and protocols, with the main objective of restricting the prescription of antibiotics.

Conclusion

In conclusion, our results have revealed antibiotics for which a high prescription rate is not rational in primary dental care in Kosovo. The prescription of antibiotics is exclusively empiric without prior sensitivity testing, which may negatively impact bacterial resistance profiles. The use of broad-spectrum antibiotics should be replaced with that of more narrow-spectrum antibiotics, and a more restrictive prescription pattern should be established. The stewardship program should include the field of dental care and should be more comprehensive.

Conflict of Interest

We hereby declare that this manuscript is original and that the work has not been published elsewhere. The authors have no conflicts of interest that are directly relevant to the content of this article.

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References

1. Falkenstein S, Stein JM, Henne K, Conrads G. Trends in antibiotic use and microbial in periodontal treatment: comparing surveys of German dentists in a ten-year period. *Clinical oral investigations.* 2016; **20**: 2203-2210.

2. Pipalova R, Vlcek J, Slezak R. The trends in antibiotic use by general dental practitioners in the Czech Republic (2006-2012). *International Dental Journal.* 2014; **64**: 138-143.

3. Gossens H. Antibiotic consumption and link to resistance. *Clinical Microbiology and Infection.* 2009; **15**: 12-15.

4. Cantón R, Horcajada JP, Oliver A, Garbajosa PR, Vila J. Innapropriate use of antibiotics in hospitals: the complex relationship between antibiotic use and antimicrobial resitance. *Enfermedades Infecciosas y Microbiología Clínica.* 2013; **31**: 3-11.

5. World Health Organization (WHO). The role of education in the rational use of medicines, SEARO Technical Publication series No.54. India, 2006.

6. Finch R. Antibiotic Resistance-from pathogen to disease surveillance. *Clinical Monitoring and infection.* 2002; **8**: 317-322.

7. World Health Organization (WHO). The World Medicines Situation 2011 - Rational Use of Medicines. Geneva, 2011.

8. Schmidt-Mende K, Hasselstrom J. Drug utilization review--a practical example from primary care. *Lakartidningen.* 2013; **110**: 1105-1107.

9. Baysari MT, Oliver K, Egan B, Li L, Richardson K, et al. Audit and feedback of antibiotic use; utilising electronic description data. *Archive of "Applied Clinical Informatics".* 2013; **4**: 583-595.

10. Bachhav SS, Kshirsagar NA. Systematic review of drug utilization studies & use of the drug classification system in the WHO-SEARO Region. *Indian Journal of Medical Research.* 2015; **142**: 120-129.

11. Versporten A, Coenen S, Adriaenssens N, Muller A, Minalu G, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient cephalosporin use in Europe (1997-2009). *The Journal of antimicrobial chemotherapy.* 2010; **66**: vi25-35.

12. World Health Organization Action Programme on Essential Drugs. How to investigate drug use in health facilities: selected drug use indicators. Geneva, World drug use indicators. Geneva, 1983.

13. World Health Organization. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2013. Geneva, 2012.

14. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision. Geneva, 2014.

15. Monnet DL, Mölstad S, Cars O. Defined daily doses of antimicrobials reflect antimicrobial prescriptions in ambulatory care. *Journal of Antimicrobial Chemotherapy.* 2004; **53**: 1109–1111.

16. Dar-Odeh NS, Abu-Hammad OA, Al-Omiri MK, Khraisat AS, Shehabi AA. Antibiotic prescribing practices by dentists: a review. *Journal of Therapeutics and Clinical Risk Management.* 2010; **6**: 301-306.

17. Rachmawati MW, Naoko YN, Hirohito TH, Kimura K. Antibiotic utilization in a dental teaching hospital in Yogyakarta, Indonesia. *Science Journal of Clinical Medicine.* 2014; **3**: 37-42.

18. Ramu C, Padmanabhan TV. Indications of antibiotic prophylaxis in dental practice- Review. *Asian Pacific Journal of Tropical Biomedicine.* 2012; **2**: 749-754.

19. Kuriyama T, Absi EG, Williams DW, Lewis MA. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *British Dental Journal.* 2005; **198**: 759–763.

20. Tenenbaum H, Jehl F, Gallion C, Dahan M. Amoxicillin and clavulanic acid concentrations in gingival cervicular fluid. *Journal of Clinical Periodontology.* 1997; **24**: 804-807.

21. Pasquantonio G, Condò S, Cerroni L, Bikiqu L, Nicoletti M, et al. Antibacterial activity of various antibiotics against oral streptococci isolated in the oral cavity. *International Journal of Immunopathology and Pharmacology.* 2012; **25**: 805-809.

22. Roda R, Bagan JV, Bielsa JM, Carbonell EP. Antibiotic use in dental practice. A review. *Medicina Oral Patologia Oral y Cirugia Bucal.* 2007; **12**: 186-192.

23. Marra F, George D, Chong M, Sutherland S, Patrick DM. Antibiotic prescribing by dentists has increased; Why? *The Journal of the American Dental Association.* 2016; **147**: 320-327.