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Assessment of the bioavailability of an antibiotic prophylactic protocol in patients undergoing third molar surgery

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Abstract. The aim of this prospective study was to determine the antibiotic bioavailability of a prophylactic protocol in patients undergoing third molar surgery. Samples from 25 patients were analysed (average age 21 ± 3.89 years, range 18–33 years; 14 female). The patients received single-dose prophylaxis of 2 g amoxicillin orally 1 hour prior to third molar surgery. Venous blood (1.5 ml) and blood from the third molar socket (1.50 ml) were obtained. The amoxicillin plasma concentration was determined in both samples by high performance liquid chromatography with a diode-array detector (HPLC/DAD). Their associations with demographic variables (age, height, weight, body mass index (BMI), sex) and antibiotic exposure time were analyzed using linear regression models. The mean amoxicillin plasma level detected in the venous blood was 1.21 ± 1.17 μg/ml (range 0.49–6.34 μg/ml) and in the third molar socket was 4.14 ± 2.24 μg/ml (range 0.86–7.46 μg/ml) ($P < 0.001$). No relationship was observed between the bioavailability of the drug and the patient biometric indices evaluated. The prophylactic administration of 2 g amoxicillin in third molar surgery showed greater bioavailability in the molar socket than the concentrations established as necessary to inhibit the growth of microorganisms that cause oral infections. The results show the need to review the current infection control protocols in oral surgery in light of the overestimated doses observed.

Key words: antibiotic prophylaxis; pharmacokinetics; oral surgical procedures; dentistry; third molar.

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Antibiotic prophylaxis in third molar surgery (TMS) is a pharmacological therapy designed to reduce postoperative complications and infections caused by microorganisms present in the oral cavity, which is considered a potentially contaminated environment[1]. To date, its use in healthy patients has been controversial due to the risk of exposure to an unsuitable dosage and bacterial resistance[2,3]. Recent randomized clinical trials[4–7] and systematic reviews[8–11] have yielded controversial

results in terms of the effectiveness of antibiotic prophylaxis to control bacteremia and postoperative complications, given that the rate of infections and complications may be due to the anatomy and position of the third molar[12], to the trauma and surgical time needed, or to the surgeon's experience[13]. This highlights the need for an exhaustive analysis of the balance between the benefits and disadvantages of antibiotics as a prophylactic measure in TMS[14].

Ascertaining the amoxicillin plasma concentration available at the surgical site could determine its real effectiveness against pathogenic causes of oral infections[15]. Using models for the quantification of antibiotic levels in gingival crevicular fluid and alveolar plasma, it has been shown in some studies that the post-prophylaxis bioavailability of a 2 g dose exceeds the established amounts needed to inhibit the growth of pathogenic microorganisms[16–19]. Yet there appear to be no reports in the literature that define the in situ bioavailability of the antibiotic prophylactic protocol in TMS and that compare the optimum doses required to control oral pathogenic microorganisms. Therefore, the aim of this study was to determine the antibiotic bioavailability of a prophylactic protocol in patients undergoing TMS.

Methods

Sample design and selection

A prospective study was conducted involving patients over 18 years of age requiring lower third molar extraction surgery; the patients were treated in the Maxillofacial Surgery Service of the School of Dentistry at the Universidad Austral de Chile. The study protocol was reviewed and approved by the Research and Ethics Committee of the Public Health Service of Valdivia, Región de Los Ríos.

Patients included in this study were categorized as ASA 1 (American Society of Anesthesiologists), with surgical characteristics of class II or III lower teeth according to the Pell and Gregory classification[20]. Patients with a previous history of local infection such as pericoronitis or hypersensitivity to penicillin derivatives were excluded. The sample size was calculated according to the average plasma concentration expected for 2 g amoxicillin given 1 hour before surgery noted in the alveolar blood (18.20 ± 10.42 μg/ml), as reported by Schüssl et al.[17], and considering an alpha error of 0.05 and a statistical power of 0.8%. A total requirement of 21 patients was established.

Drug protocol and surgical procedure

The patients who fulfilled the inclusion criteria and agreed to participate in the study received the prophylactic protocol of 2 g amoxicillin (Amoval; Laboratorios Saval S.A., Santiago de Chile, Chile), orally, 1 hour prior to the surgical procedure. For oral asepsis, the patients rinsed with 15 ml of 0.12% chlorhexidine digluconate solution. Local anaesthesia was administered via lower alveolar nerve block with reinforcement to the lingual nerve and superficial cervical plexus, using 2% lidocaine hydrochloride with 1:100.000 epinephrine (Lignospan; Septodont, Cambridge, Ontario, Canada).

To control for intervention bias, all surgical procedures were performed by one specialist in maxillofacial surgery with more than 15 years of experience in TMS, using a surgical protocol based on previously described recommendations[21]. The surgery consisted of a mucoperiosteal flap and osteotomy of the mandibular alveolar area with irrigation using 0.90% saline. The tooth was removed using a straight elevator and curved forceps on the edge, or by tooth sectioning when necessary. For the extraction of the blood sample from the site of the third molar socket, a relative isolation was done using sterile gauze, extracting a local sample of 1.50 ml accumulated at the surgical site. Then, the head nurse in the operating room extracted 1.50 ml of venous blood from the patient's right arm. Both samples were preserved in 2 ml tubes containing heparin (50 μg/ml). The wound was closed with 3–0 Vicryl suture (Johnson&Johnson), achieving local haemostasis with a sterile gauze compress. Postoperative pain was managed with 400 mg ibuprofen every 8 hours for 3 days if required.

Sample preparations and chromatographic measurement

All samples were prepared and analyzed at the Pharmacy Institute of the Universidad Austral de Chile. The high performance liquid chromatography with a diode-array detector (HPLC/DAD) chromatographic system used in this study included a Prominence Modular system (Shimadzu Co., Kyoto, Japan), detector (DAD, 230 nm), autosampler, and an oven for the chromatographic column at 30°C. A C18 analytical column (250 mm × 4.6 mm × 5 μm particle size) was selected. The reference standard for amoxicillin was obtained from Dr. Ehrenstorfer (Augsburg, Germany) and the other preparatory solvents were purchased from Merck (Darmstadt, Germany). The chromatographic analysis software used was Shimadzu LC Solution. For the mobile phase, isocratic solutions of phosphate buffer (0.01 M) and acetonitrile (95:5 v/v) were used, with a flow rate of 1.30 ml/min. The patient samples were prepared by centrifugation and processed with methanol cooled to 20°C for deproteinization, and centrifuged at 14.000 rpm for 30 minutes to ensure the sedimentation of proteins.

Data analysis

All data were evaluated for normality using the Shapiro–Wilk test. The baseline data of the participants were analyzed according to sex. The plasma concentrations obtained in the venous plasma and third molar socket were compared by unpaired *t*-test. In order to determine the effect of age, height, weight, body mass index (BMI), and the time between ingesting the antibiotic and taking the blood samples on the observed plasma concentrations, all data were submitted to linear regression models and Pearson's test. The significance level was set at 5% for all tests, which were performed using Stata version13.0 (StataCorp., College Station, TX, USA).

Results

Thirty patients volunteered. However, the blood samples were correctly processed for only 25 of these patients (average age 21 ± 3.89 years, range 18–33 years; 14 female). All baseline data had a normal distribution ($P < 0.05$). The characteristics of the patients according to sex are given in Table 1.

The average amoxicillin concentration in the venous plasma from the arm was 1.21 ± 1.17 μg/ml (range 0.49–6.34 μg/ml), while the average concentration in the third molar socket was 4.14 ± 2.24 μg/ml (range 0.86–7.46 μg/ml); the difference observed was statistically significant ($P < 0.001$) (Table 2).

Only a weak significant correlation was noted between the participants' height and the plasma amoxicillin concentration obtained in the third molar socket ($r = 0.44$; $P = 0.02$) (Table 3). The linear regression models using the venous plasma concentration from the arm ($F = 0.45$; $P = 0.8$) and from the third molar socket ($F = 1.37$; $P = 0.27$) were not significant.

Table 1. Baseline data of the patients participating in this study according to sex; mean ± standard deviation values.

	Female ($n=14$)	Male ($n=11$)	Total ($n=25$)	P-value[a]
Age (years)	21± 1.10	21.50 ± 1	21 ± 3.89	0.76
Height (m)	1.63 ± 0.02	1.73 ± 0.02	1.67 ± 0.10	0.00
Weight (kg)	61 ± 3.10	75.60 ± 4.30	68.30 ± 14.80	0.01
BMI (kg/m^2)	23 ± 1.10	25.30 ± 1.40	24.40 ± 4.50	0.21
Sample collection time (min)	109.60 ± 3.40	113.60 ± 4.20	111 ± 13.40	0.46

BMI, body mass index.
[a] Unpaired t-test with Welch's correction.

Table 2. Amoxicillin plasma concentrations (μg/ml) in the two blood samples, according to sex; mean ± standard deviation values.

Place of measurement	Female ($n=14$)	Male ($n=11$)	Total ($n=25$)	P-value[a]
Venous plasma	1.32 ± 0.40	0.99 ± 0.11	1.21 ± 1.17	0.21
Third molar socket	3.30 ± 0.48	5 ± 0.70	4.14 ± 2.24	0.46

[a] Unpaired t-test with Welch's correction.

Therefore, the plasma concentrations do not depend on the study variables. These models are detailed in Tables 4 and 5.

Discussion

Antibiotic prophylaxis with amoxicillin has been used widely in TMS to achieve concentrations sufficient to fight microorganisms that can colonize the surgical site[8]. In this study, the blood samples obtained from patients treated with the prophylactic antibiotic protocol of 2 g amoxicillin administered orally 1 hour before surgery showed a bioavailability in the venous blood and third molar socket, with no relationship between the concentrations and the patients' biometric variables. Furthermore, the oral administration route was demonstrated to be appropriate, allowing the drug exposure and absorption to be determined locally. According to the literature, intravenous administration may be an alternative drug therapy in cases of non-resolving infection in patients who are non-adherent to the regimen[22].

In oral surgery, prophylactic therapy with 2 g amoxicillin is the protocol most frequently considered in TMS[8]. Amoxicillin is a well-known amino-substituted penicillin with a broad antibacterial spectrum and good bioavailability, and an oral dose of 500 mg produces plasma concentrations of approximately 5.30 μg/ml within the first hour[23]. Reports of similar studies have described antibiotic plasma concentrations using prophylactic protocols of amoxicillin 1 hour prior to sample collection in alveolar plasma[17,24], in blood serum[25], and in crevicular fluid[26]. The importance of determining sufficient plasma concentrations of the antibiotic in the alveolus after TMS is useful for evaluating the potential bactericidal effects produced and for making a comparison to the minimum inhibitory concentration (MIC) needed to fight pathogens that cause oral infections[2]. It must be emphasized that the bioavailability found in this study included values in excess of those advocated as necessary to inhibit the microorganisms that cause oral infections[19]. The MIC values for some such microorganisms are as follows: *Porphyromonas gingivalis*, MIC_{90} ≤0.25 μg/ml[16]; *Bacteroides forsythus*, MIC_{90} 0.50 μg/ml[18]; *Prevotella spp*, MIC_{90} 0.25 μg/ml[16,19]; *Fusobacterium spp*, MIC_{90} ≤0.25 μg/ml[16]; *Parvimonas micra,* MIC_{90} 0.12 μg/ml, respectively. Considering that the effectiveness of antibiotics is achieved in a range two to four times greater than the

Table 3. Linear correlation between the study variables (Pearson test, Pearson's r values).

Sample	Age	Height	Weight	BMI	Blood collection time	Venous plasma
Venous plasma	0.06 ($P=0.7$)	−0.24 ($P=0.2$)	−0.05 ($P=0.8$)	0.06 ($P=0.7$)	−0.02 ($P=0.9$)	–
Third molar socket	0.03 ($P=0.87$)	0.44 ($P=0.02$)	0.13 ($P=0.53$)	−0.08 ($P=0.7$)	−0.04 ($P=0.8$)	0.16 ($P=0.4$)

BMI, body mass index.

Table 4. Linear regression analysis of the patient variables fit to the venous blood plasma concentration.

Variable	Non-standardized coefficient (B)	Error	Standardized coefficient (Beta)	t	P-value	95% CI for B	
Sex	2.17	0.89	0.50	1.41	0.26	0.28	4.05
Age	0.03	0.12	0.06	0.28	0.77	−0.22	0.30
BMI	−0.12	0.11	−0.24	−1.10	0.28	−0.34	0.11
Blood collection time	−0.01	0.03	−0.08	−0.38	0.71	−0.08	0.05
Venous plasma	0.47	0.38	0.25	1.24	0.22	−0.32	1.28
Constant	6.11	5.02	–	1.22	0.23	−4.41	16.64

CI, confidence interval; BMI, body mass index.

Table 5. Linear regression analysis of the patient variables fit to the blood plasma concentration in the third molar socket.

Variable	Non-standardized coefficient (B)	Error	Standardized coefficient (Beta)	t	P-value	95% CI for B	
Sex	−0.71	0.56	−0.31	−1.25	0.22	−1.9	0.47
Age	0.00	0.07	0.02	0.08	0.93	−0.14	0.15
BMI	0.04	0.06	0.16	0.63	0.53	−0.09	0.17
Blood collection time	0.00	0.02	0.03	0.16	0.87	−0.03	0.04
Third molar socket	0.15	0.12	0.30	1.24	0.22	−0.10	0.42
Constant	−0.60	2.99	–	−0.20	0.84	−6.87	5.67

CI, confidence interval; BMI, body mass index.

MIC reported[27], the concentrations observed are substantially greater than those required for the bacteria associated with oral and maxillofacial infections. This means that patients are being exposed to higher doses of the drug than those required, and with antibiotics exceeding the MIC there is selective enrichment of mutant pathogens[28], contributing to changes in the susceptibility of the bacteria to antibiotics[29].

With respect to the participants' biometric characteristics, no association with or dependency on the amount of antibiotic in the third molar socket and venous plasma samples was observed. Nevertheless, the concentration detected in the third molar socket was statistically greater than that in the venous plasma ($P < 0.001$). This result may be due to the amoxicillin binding to the proteins present in the plasma, generating a fraction smaller than that available in interstitial tissues like the third molar alveolus, influencing the extent of the bioavailability and the penetration of antibiotics into the lymph and interstitial space[30].

The lack of evidence to clarify this issue has caused dentists in different countries to prescribe non-ideal prophylactic doses of antibiotics[6,10,11]. Statistical analyses of effectiveness according to the number needed to treat (NNT) have shown that between 40[8] and 96[7] patients must be medicated to avoid one postoperative infection, and at least 38[14] for the treatment of alveolar osteitis. These data confirm the need to limit the use of high prophylactic doses of amoxicillin for TMS, owing mainly to the low incidence of postoperative infection, young age of the patients, and the fact that the patients are healthy (mostly the case for patients requiring TMS), as well as the aseptic technique under which the surgery is performed[4] and the self-limiting nature of infections in the oral cavity[31]. The 2008 recommendations of the National Institute for Health and Care Excellence[32] did not include antibiotic prophylaxis for any dental procedure regardless of the patient's history, focusing treatment on educating the patient and controlling dental biofilm combined with the use of oral antiseptics like chlorhexidine[33].

The limitations of this study are related to possible biases in the sampling due to the probability of contamination of the alveolus sample with saliva during its extraction. The expert surgeon controlled this point by using relative isolation with sterile gauze and the least intervention possible with saline in the cleaning of the surgical wound. Despite these limitations, it was possible to show the current situation for patients exposed to the treatment regimens adopted in dentistry to control postoperative infection. The results show that current infection control protocols in oral surgery require review, and that we are exposing patients to protocols with overestimated doses.

In conclusion, further studies are required to analyze the serial concentrations of different prophylactic antibiotic regimens, routes of administration, and minimum inhibitory concentrations for different strains of microorganisms, as well as longitudinal studies to observe the presence of infections and the real expression of periodontopathogenic bacteria present at the surgical site.

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Competing interests

None.

Ethical approval

Approved (Ord No. 074/2015).

Patient consent

Patient consent was obtained.

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References

1. Halpern LR, Dodson TB. Does prophylactic administration of systemic antibiotics prevent postoperative inflammatory complications after third molar surgery? *J Oral Maxillofac Surg* 2007;**65**:177–85. http://dx.doi.org/10.1016/j.joms.2006.10.016.
2. González Navarro B, Jané Salas E, Estrugo Devesa A, López López J, Viñas M. Bacteremia associated with oral surgery: a review. *J Evid Based Dent Pract* 2017;**17**:190–204. http://dx.doi.org/10.1016/j.jebdp.2016.12.001.
3. Oberoi SS, Dhingra C, Sharma G, Sardana D. Antibiotics in dental practice: how justified are we. *Int Dent J* 2015;**65**:4–10. http://dx.doi.org/10.1111/idj.12146.
4. Milani BA, Bauer HC, Sampaio-Filho H, Horliana AC, Perez FE, Tortamano IP, Jorge WA. Antibiotic therapy in fully impacted lower third molar surgery: randomized three-arm, double-blind, controlled trial. *Oral Maxillofac Surg* 2015;**19**:341–6. http://dx.doi.org/10.1007/s10006-015-0521-6. Epub 2015 Aug 13.
5. Reiland MD, Ettinger KS, Lohse CM, Viozzi CF. Does administration of oral versus intravenous antibiotics for third molar removal have an effect on the incidence of alveolar osteitis or postoperative surgical site infections? *J Oral Maxillofac Surg* 2017;**75**:1801–8. http://dx.doi.org/10.1016/j.joms.2017.03.038.
6. Sidana S, Mistry Y, Gandevivala A, Motwani N. Evaluation of the need for antibiotic prophylaxis during routine intra-alveolar dental extractions in healthy patients: a randomized double-blind controlled trial. *J Evid Based Dent Pract* 2017;**17**:184–9. http://dx.doi.org/10.1016/j.jebdp.2017.04.007.
7. Xue P, Wang J, Wu B, Ma Y, Wu F, Hou R. Efficacy of antibiotic prophylaxis on postoperative inflammatory complications in Chinese patients having impacted mandibular third molars removed: a split-mouth, double-blind, self-controlled, clinical trial. *Br J Oral Maxillofac Surg* 2015;**53**:416–20. http://dx.doi.org/10.1016/j.bjoms.2015.02.001.
8. Arteagoitia MI, Barbier L, Santamaría J, Santamaría G, Ramos E. Efficacy of amoxicillin and amoxicillin/clavulanic acid in the prevention of infection and dry socket after third molar extraction. A systematic review and meta-analysis. *Med Oral Patol Oral Cir Bucal* 2016;**21**:e494–504.
9. Isiordia-Espinoza MA, Aragon-Martinez OH, Martínez-Morales JF, Zapata-Morales JR. Risk of wound infection and safety profile of amoxicillin in healthy patients which required third molar surgery: a systematic review and meta-analysis. *Br J Oral Maxillofac Surg* 2015;**53**:796–804. http://dx.doi.org/10.1016/j.bjoms.2015.06.013.
10. Kreutzer K, Storck K, Weitz J. Current evidence regarding prophylactic antibiotics in head and neck and maxillofacial surgery. *Biomed Res Int* 2014;**2014**:879437.
11. Marghalani A. Antibiotic prophylaxis reduces infectious complications but increases adverse effects after third-molar extraction in healthy patients. *J Am Dent Assoc* 2014;**145**:476–8. http://dx.doi.org/10.14219/jada.2013.51.
12. Alvira-González J, Figueiredo R, Valmaseda-Castellón E, Quesada-Gómez C, Gay-Escoda C. Predictive factors of difficulty in lower third molar extraction: a prospective cohort study. *Med Oral Patol Oral Cir Bucal*

2017;**22**:e108–14. http://dx.doi.org/10.4317/MEDORAL.21348.

13. Ramos E, Santamaría J, Santamaría G, Barbier L, Arteagoitia I. Do systemic antibiotics prevent dry socket and infection after third molar extraction? A systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2016;**122**:403–25. http://dx.doi.org/10.1016/j.oooo.2016.04.016.
14. Lodi G, Figini L, Sardella A, Carrassi A, Del Fabbro M, Furness S. Antibiotics to prevent complications following tooth extractions. *Cochrane Database Syst Rev* 2012;**11**. http://dx.doi.org/10.1002/14651858.CD003811.pub2. CD003811.
15. Aravena P, Oyarzún C, Arias M, Monardes H, Jerez A, Benso B. Single-dose bioavailability for prophylactic coverage in patients undergoing dental implant surgery. *Int J Oral Maxillofac Implants* 2018;**33**:419–24. http://dx.doi.org/10.11607/jomi.5943.
16. Eick S, Pfister W, Straube E. Antimicrobial susceptibility of anaerobic and capnophilic bacteria isolated from odontogenic abscesses and rapidly progressive periodontitis. *Int J Antimicrob Agents* 1999;**12**:41–6.
17. Schüssl Y, Pelz K, Kempf J, Otten JE. Concentrations of amoxicillin and clindamycin in teeth following a single dose of oral medication. *Clin Oral Investig* 2014;**18**:35–40. http://dx.doi.org/10.1007/s00784-013-0958-7.
18. Takemoto T, Kurihara H, Dahlen G. Characterization of *Bacteroides forsythus* isolates. *J Clin Microbiol* 1997;**35**:1378–81.
19. Veloo ACM, van Winkelhoff AJ. Antibiotic susceptibility profiles of anaerobic pathogens in The Netherlands. *Anaerobe* 2015;**31**:19–24. http://dx.doi.org/10.1016/j.anaerobe.2014.08.011.
20. Pell GJ, Gregory GT. Report on a ten-year study of a tooth division technique for the removal of impacted teeth. *Am J Orthod Oral Surg* 1942;**28**:B660–6. http://dx.doi.org/10.1016/S0096-6347(42)90021-8.
21. Hupp J, Tucker M, Ellis E. *Contemporary oral and maxillofacial surgery*. 7th Edition. Mosby; 2019.
22. Béïque L, Zvonar R. Addressing concerns about changing the route of antimicrobial administration from intravenous to oral in adult inpatients. *Can J Hosp Pharm* 2015;**68**:318–26.
23. Suarez-Kurtz G, Ribeiro FM, Vicente FL, Struchiner CJ. Development and validation of limited-sampling strategies for predicting amoxicillin pharmacokinetic and pharmacodynamic parameters. *Antimicrob Agents Chemother* 2001;**45**:3029–36. http://dx.doi.org/10.1128/AAC.45.11.3029-3036.2001.
24. Wexell C, Ryberg H, Sjöberg Andersson WA, Blomqvist S, Colin P, Van Bocxlaer J, Dahlén G. Antimicrobial effect of a single dose of amoxicillin on the oral microbiota. *Clin Implant Dent Relat Res* 2016;**18**:699–706. https://doi.org/10.1016/j.ijom.2017.02.935.
25. Khoury SB, Thomas L, Walters JD, Sheridan JF, Leblebicioglu B. Early wound healing following one-stage dental implant placement with and without antibiotic prophylaxis: a pilot study. *J Periodontol* 2008;**79**:1904–12. http://dx.doi.org/10.1902/jop.2008.070670.
26. Tenenbaum H, Jehl F, Gallion C, Dahan M. Amoxicillin and clavulanic acid concentrations in gingival crevicular fluid. *J Clin Periodontol* 1997;**24**:804–7.
27. Vincent JL, Abraham E, Kochanek P, Moore FA, Fink MP. *Textbook of critical care*. Elsevier Health Sciences; 2011.
28. Zhao X, Drlica K. Restricting the selection of antibiotic-resistant mutant bacteria: measurement and potential use of the mutant selection window. *J Infect Dis* 2002;**185**:561–5. http://dx.doi.org/10.1086/338571.
29. Blondeau JM. New concepts in antimicrobial susceptibility testing: the mutant prevention concentration and mutant selection window approach. *Vet Dermatol* 2009;**20**:383–96. http://dx.doi.org/10.1111/j.1365-3164.2009.00856.x.
30. Woodnutt G, Berry V, Mizen L. Effect of protein binding on penetration of beta-lactams into rabbit peripheral lymph. *Antimicrob Agents Chemother* 1995;**39**:2678–83.
31. Calvo AM, Brozoski DT, Giglio FP, Gonçalves PZ, Sant'ana E, Dionísio TJ, Lauris JR, Santos CF. Are antibiotics necessary after lower third molar removal? *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;**114** (5 Suppl):S199–208. https://doi: 10.1016/j.oooo.2011.10.022.
32. *Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures*. London, UK: National Institute for Health and Clinical Excellence; 2008.
33. Rodríguez Sánchez F, Rodríguez Andrés C, Arteagoitia Calvo I. Does chlorhexidine prevent alveolar osteitis after third molar extractions? Systematic review and meta-analysis. *J Oral Maxillofac Surg* 2017;**75**:901–14. http://dx.doi.org/10.1016/j.joms.2017.01.002.

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