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Review Article

Update in Antibiotics Prophylaxis in Oral Surgery: A Systematic Review

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ABSTRACT

Background: Antibiotic prophylaxis has become a controversial topic in the field of dentistry and their usage has been strongly debated. In oral surgery, the controversy arises in healthy patients as the inappropriate use of antibiotics is becoming a major concern in our society. The purpose of this study is thus, to evaluate the efficacy of antibiotic prophylaxis in preventing postoperative complications in oral surgery.
Material and Methods: An electronic search in the Cochrane Library, PubMed (MEDLINE) and Science Direct data- bases was conducted between September 2019 and November 2019 by two observers. Eleven studies qualified for the systematic review.
Results: Results suggest that the usage of amoxicillin in combination with clavulanic acid as antibiotic prophylaxis in oral surgery should not be considered as the adverse reactions are too high. In the other hand, amoxicillin is a safe option in antimicrobial prophylaxis in oral surgery. However, Gastrointestinal disturbances accounted for a significant proportion of the adverse reactions recorded for all antibiotics examined, special consideration is needed in the administration of antibiotic prophylaxis in patients with gastrointestinal problems.
Conclusions: The usage of prophylactic antibiotic therapy in oral surgery is not effective and doesn´t improve the overall results of the surgical intervention.
Keywords: antibiotic prophylaxis; oral surgery; third Molar; meta-analysis; adverse effects; amoxicillin; amoxicillin–potassium clavulanate combination.

1. INTRODUCTION

Antibiotic prophylaxis plays a key role in preventing inflammatory processes of odontogenic and systemic infections. However, it has become a controversial topic since from 2006 it was shown that between 10 and 12% of prescribed antibiotics were for dental use [1] and not all dental procedures have the same risk of bacterial infection, since it is conditioned by the type of wound and the pathology of the patient [2]. Nowadays, the use of antibiotic prophylaxis in dentistry has been strongly debated. Within the field of dentistry, a greater number of discrepancies have

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been observed when establishing antibiotic prophylaxis or not in oral surgery. Some studies on third molar extractions, indicate that there were statistically significant differences in those groups that were prescribed 5-day postoperative or single dose preoperative antibiotic prophylaxis with a dose of 2gr / 125mg amoxicillin / clavulanic acid than those in placebo groups, with a decrease in both inflammatory and intra and post-operative infections [3].

The controversy arises because prophylactic antibiotic therapy is usually not indicated in healthy patients, and the inappropriate use of antibiotics contributes to the development of antibiotic resistance.

Although beta-lactams antibiotics have become the prophylactic antibiotics par excellence, for allergic patients the antibiotic of choice is clindamycin. It has a greater range of action than penicillin and other beta-lactams antibiotics, especially in dentoalveolar infections because one of the main advantages of clindamycin is the stimulation of the immune system. [4] On the other hand, it involves greater penetration at the bone level compared to other antibiotics [5, 6]. Although it is considered the ideal antimicrobial in the treatment of acute dentoalveolar abscesses, it is not used in odontogenic abscesses because it causes pseudomembranous colitis [7].

The extraction of the third molar, despite being the most common intervention in oral surgery, no studies have been found that providestandardized protocols for the clinician in the use of antibiotic prophylaxis.

The purpose of this study is thus, to evaluate the efficacy of antibiotic prophylaxis in preventing postoperative complications such as: fever, swelling, pain, and wound infection.

2. MATERIAL AND METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses declaration. (8)An electronic search in the Cochrane Library, PubMed (MEDLINE) and ScienceDirect data- bases was conducted between September 2019 and November 2019. The designed search strategy was:

Pubmed: (tooth[MeSH Terms]) AND bacterial infections[MeSH Terms])) OR periapical abscesses[MeSH Terms]) OR periodontal abscess[MeSH Terms]) OR infection control, dental[MeSH Terms]) OR pericoronitis[MeSH Terms]) OR odontogenic infections[Title/Abstract]) AND anti-bacterial agents[MeSH Terms]

Scopus: (tooth[MeSH Terms]) AND bacterial infections[MeSH Terms])) OR periapical abscesses[MeSH Terms]) OR infection control, dental[MeSH Terms]) OR pericoronitis[MeSH Terms]) OR odontogenic infections[Title/Abstract]) AND anti-bacterial agents[MeSH Terms]

Cochrane: (tooth AND bacterial infections) OR periapical abscesses OR periodontal abscess OR infection control, dental OR pericoronitis OR odontogenic infections AND anti-bacterial agents

PICO Question

The (Participant, Intervention, Comparison, Outcome) PICO question of this study was “Are prophylactic antibiotic therapy effective at infections and adverse reactions in patients without uncontrolled systemic diseases” ?.

In addition, a manual search was performed in the following journals: In addition, a manual search of the studies published in the last 10 years was carried out in the following journals: *Research Journal of Pharmaceutical, Biological and Chemical Sciences, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, Journal of Oral and Maxillofacial Surgery, Antimicrobial Agents and Chemotherapy, British Journal of Oral and Maxillofacial Surgery, Medicina Oral Patologia Oral y Cirugia Bucal*
for identify possible eligible items not included in the electronic search.

Study Selection

Two independent examiners (A.C.C. and B.G.X.) selected the articles according to the inclusion criteria. A third reviewer (J.L.Q.) resolved any discrepancies.

A Cohen kappa for each database was calculated to determine the interrater reliability.

After the review of the title, the summary was read and finally those articles that after the evaluation of the full text did not meet the pre-established inclusion criteria were excluded.

The following inclusion criteria were used in the presentstudy was randomized clinical trials, performed on humans and published within the last 10 years (2009–2019). No language restriction was applied. The exclusion criteria were nonhuman studies, prospective or retrospective cohort studies, and cross-sectional studies review articles, case series, case reports, and studies based on surveys or expert opinions. The selected articles were classified into different levels of evidence with the Scottish Intercollegiate Guidelines Network (SIGN)(9). Moreover, the risks of bias of randomized clinical trials were independently assessed using the Cochrane Tool RoB 2. [10] The characteristics collected from the studies in order to perform a qualitative analysis were based on the type of antibiotics, dose and duration, post-operative outcome, follow-up, number of infections reported, and adverse outcomes related to antibiotic use.

3. RESULTS

The flowchart according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines is provided in Figure 1.

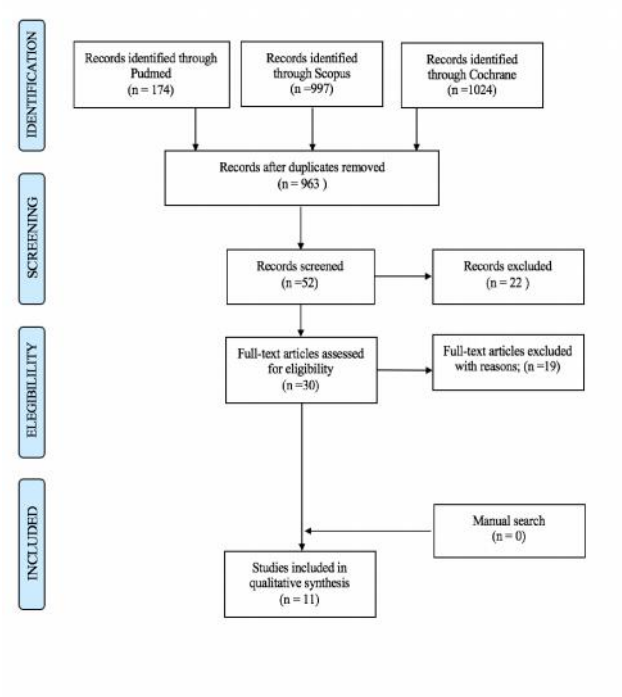

Fig 1: A flowchart of articles according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Description and selection of studies

The search in the three electronic databases obtained a total of 450 studies. After evaluating the articles according to the inclusion and exclusion criteria and eliminating duplicates, the full text of 30 studies was analyzed. The Cohen kappa was 1 for the Cochrane Library, 0.78 for PubMed, and 0.84 for Scopus. After reading the complete articles, 18 of them were excluded [11-28].

Finally, 11 articles were chosen to be included in this systematic review: 11 randomized clinical trials [29-39] with three of them in split mouth design.

Concretely, the clinical articles were grouped into a table recording type of antibiotic, dose and duration, sample size, postoperative outcome, follow-up, number the cases with infections and adverse outcomes.

Table 1: Studies selection and level of evidence SIGN

Author	Year	Type of study	SampleSize	Protocols	SIGN	Grade of recommendation
Luances-Rey et al. (29)	2010	RCT	160	Twoamoxicill in different protocols	1++	A
Siddiqi et al. (30)	2010	RCT, Split mouth	100	Amoxicillin VS. Placebo	1-	B
Bezerra et al. (31)	2011	RCT, Split mouth	800	Amoxicillin VS. Placebo	1+	A
L-Cedrun et al. (32)	2011	RCT	123	Two amoxicillin different protocols VS. Placebo	1++	A
Pasupathy et al. (33)	2011	RCT	89	Amoxicillin VS. Metronidazole VS. Placebo	1-	B
Bortoluzzi et al. (34)	2013	RCT	50	Two amoxicillin different protocols VS. Placebo	1++	A
Arteagoitia et al. (35)	2015	RCT	118	Amoxicillin VS. Placebo	1+	A
Milani et al. (36)	2015	RCT	80	Two different routes of amoxicillin VS. Placebo	1-	B
Xue et al. (37)	2015	RCT, Split mouth	207	Amoxicillin VS. Placebo	1-	B
Kenevick et al. (38)	2018	RCT	400	Amoxicillin VS. Placebo	2++	C

Risk of bias assessment

The results of the risks of bias assessment are shown in figures 2 and 3. Selection bias were assessed as low in the studies in the random sequence generation by 7 studies [29-31, 33-35, 37] but 1 study [32], due to inadequate evaluation of the randomization describe high risk of bias. Nevertheless, due to the allocation concealment only five studies describe low risk of bias [29-31, 34, 37], meanwhile Kenevick *et al* [39], Milani *et al* [36] and Pasupathy *et al* [33] displayed high risk.

For detection bias, only 2 studies [33, 39] showed high risks due to the impossibility from the examiners of describing the blinding of the participants and outcome assessment.

The attrition bias was the worst parameter assessed as high risk with 6 studies [31,39,38,33,30,37]. Three studies [39,30,37] showed high risk of reporting bias. Other risks of bias were considered high or unclear in nine studies. Overall, all included studies were at high risk of bias for at least one domain (table 2).

In our evaluation, it was included a total of 11 studies with 1456 patients. The parameters evaluated were swelling, edema, alveolitis, infection, inflammation and pain. Three of the studies were split-mouth clinical trial, [30, 31, 37] but only Xue *et al.* described adverse reactions such gastrointestinal infections with at least 10 days of follow up. Two studies evaluate 2 different antibiotic options like metronidazole 800mg [33], clindamycin 300mg [37]. In the amoxicillin group, 4 studies did not refer any case of infection [31, 32, 34, 39], meanwhile the placebo group expressed infection in all the studies except in the Kenevick *et al* [39] in a pericoronal infection.

4. DISCUSSION

Summary of evidence

This systematic review was meant to focus on the efficiency of the antibiotic prophylaxis in oral surgery procedures. Our review showed, that many variables influence in the effectiveness of the antibiotic.

Regarding the doses, 5 studies prescribed 2gr of amoxicillin before the surgical intervention [29, 32, 34, 35, 38]. These studies registered a mean of 8'3% of infection in the study group. Moreover, Arteogoitia *et al.*, also evaluated cases of adverse reactions with a 20% of the cases.

Table 2: Studies Included in this Systematic Review

Author Year	Antibiotics: Dose and duration	Sample size	Postoperative outcomes	Follow-up appointments	Number of cases reporting with infections	Adverse outcomes related to antibiotic use
Luances-Rey *et al* 2010	Group 1: 2 g AMX 1 hour before surgery and 1 g AMX 6 hours after surgery.	160	Alveolitis	1 week	Group 1: 3/50	No adverse reactions reported
	Group 2: 1 g of AMX 6 h after surgery followed by 1 g AMX every 8 hour for 4 days.		Surgical infection		Group 2: 4/75	
	(SameTablets using Placebo)		Nº of analgesic needed			
			Subjective pain scale			
			Post-surgical inflammation			
			Consistency of diet			
			Temperature			
			Millimeters of mouth opening loss			
Siddiqi *et al* 2010	Group 1: First visit: Oral AMX 1g at 1h preoperative; second visit (3 weeks later) placebo 1 g at 1 hour before surgery, or vice versa.	95	Pain	3 days	AMX and placebo: 1	No adverse reactions reported
	Group 2: first visit: oral AMX 1g at 1 hour preoperative and AMX 500mg 8 hourly for 2 days after surgery: second visit (3 weeks later) placebo under the same regimen or vice versa.		Swelling	1 week	AMX no placebo: 1	
			Infection	2 weeks	Placebo no AMX: 3	
			Trismus		No infection: 90	
			Temperature rising			
Bezerra *et al* 2011	Group E: AMX two 500mg capsules 1h before surgery	34	Soft tissue edema pain	3 Days	AMX and placebo: 0	No adverse reactions reported
	Group C: placebo (Starch) Two 500mg capsules before surgery		Limitation of mouth opening	1 week	AMX no placebo: 1	
			Presence of purulent secretion	2 weeks	Placebo no AMX: 4	
			Alveolitis		No infection: 29	
L-Cedrun *et al* 2011	Group A: AMX 500mg (Clamoxyl) 4 tablets 2h before surgery	123	Pain	4 weeks	Group A: 0/39	Group A: 7/39
	Group B: Placebo		Wound infection		Group B: 5/40	Group B: 4/40
	Group C: AMX 500mg three times a day for 5 days		Trismus		Group C: 0/44	Group C: 6/44
			Temperature rising			
			Intra- and extraoral swelling			
			Swelling			
			Dysphagia			
			Side effects			
Pasupathy *et al* 2011	E1: oral AMX 1g at 1h before surgery	89	Increase in body temperature	7 days	E1: 2/31	No adverse reactions reported
	E2: oral metronidazole 800mg at 1h before surgery		Purulent discharge from the wounds		E2: 0/29	
	C: Placebo				C: 3/29	
Bortoluzzi *et al* 2013	Group 1 (G1) included a prophylactic dose of 2 g of amoxicillin and 8 mg of dexamethasone.	50	Alveolar osteitis	5 days	G1: 0/ 12	No adverse reactions reported

	Group 2 (G2) included a prophylactic dose of 2 g of amoxicillin and 8 mg of placebo.		Alveolar infection		G2: 1/12	
	Group 3 (G3) included a prophylactic dose of 8 mg of dexamethasone and 2 g of placebo.		Pain		G3: 1/14	
	Group 4 (G4) placebo.		Trismus		G4: 1/12	
			Edema			
Arteagoitia *et al* 2015	Group EG: 2 g AMX/125 mg CLA at 2 hours before surgery; postoperatively twice a day for 4 days.	118	Pain	1week	Group EG: 2/60	Group EG: 12/60
	Group CG: Placebo		Edema	Up to 8 weeks	Group CG: 5/58	Group CG: 1/58
			Mouth opening			
			Abscess			
			Alveolitis			
			Dehiscence			
Milani *et al* 2015	Group 1 (G1), amoxicillin (1 g) 1 h before surgery + 500 mg 1/8 h for 7 days.	80	Mouth opening	Baseline	Group 1: 1/30	No adverse reactions reported
	Group 2 (G2), 1-g amoxicillin 1 h before surgery plus placebo, with identical appearance to G1, 1/8 h for 7 days.		Facial edema and	4 days	Group 2: 3/30	
	Group 3 (G3), placebo 1 h before surgery and 500 mg 8/8 h for 7 days.		Pain	7 days	Group 3: 0/20	
			Body temperature			
			Lymphadenopathy			
			Dysphagia			
			Infection			
Xue *et al* 2015	Group 1: amoxicillin (or clindamycin) was given (antibiotic group) one hour before operation	207	Alveolar osteitis	2 days	Group 1: 6/192	Group 1: 4 Gastrointestinal reaction
	until 3 days postoperatively.		Surgical wound infection	10 days	Group 2: 8/192	Group 2: None
	Group 2: placebo was given (placebo group) at the same time.		Peribuccal infection			
			Infection of the anterior isthmus of fauces			
			Bleeding			
			Ulcers			
			Fever			
			Gastrointestinal reaction			
Kenevick *et al* 2018	Group 1: No pericoronal inflammation, 2 g AMX 1 hour before surgery	400	Swelling	1 day	G1: 0/ 100	No adverse reactions reported
	Group 2: No pericoronal inflammation, placebo 1 hour before surgery		Alveolar osteitis	7 days	G2: 0/100	
	Group 3: Pericoronal inflammation, 2 g AMX 1 hour before surgery		Infection		G3: 0/100	
	Group 4: Pericoronal Inflammation, placebo 1 hour before surgery		Limited mouth opening		G4: 0/100	
			Pain			
			Bleeding			
			Increased body temperature			

Table 3: A list of articles excluded and the reasons for exclusion

Author	Exclusion criteria
Chardin *et al* (11)	This publication did not evaluate antibiotic prophylaxis
Al Nawas *et al* (12)	This publication did not evaluate antibiotic prophylaxis
Majectic *et al* (13)	This publication did not evaluate antibiotic prophylaxis
Cachovan *et al* (14)	This publication did not evaluate antibiotic prophylaxis
Sisalli *et al* (15)	Lettertothe editor
Sobotkka *et al* (16)	This publication did not evaluate antibiotic prophylaxis
Rui figueiredo *et al* (17)	This publication only evaluated bacteriological parameters
Lee *et al* (18)	This publication evaluated different surgical techniques.
Iglesias Martin *et al* (19)	Subjective postoperative follow- up (phone calls...)
Igoumenkis *et al* (20)	This publication did not evaluate antibiotic prophylaxis
Zirk *et al* (21)	This publication did not evaluate antibiotic prophylaxis
Bali *et al* (22)	This publication did not evaluate antibiotic prophylaxis
Bramaih *et al* (23)	Subjective postoperative follow-up (life quality questionnaire)
Adde *et al* (24)	Subjective postoperative follow-up (phone calls...)
Durall *et al* (25)	This publication evaluated the interaction of the Chlorhexidine and amoxicilin.
Crincoli *et al* (26)	This publication evaluated different administration of the antibiotic.
Monaco *et al* (27)	No Randomised Clinical Trial.
Kumari *et al* (28)	This publication evaluated different surgical techniques.
Natarajan *et al* (29)	This publication did not evaluate antibiotic prophylaxis only postoperative

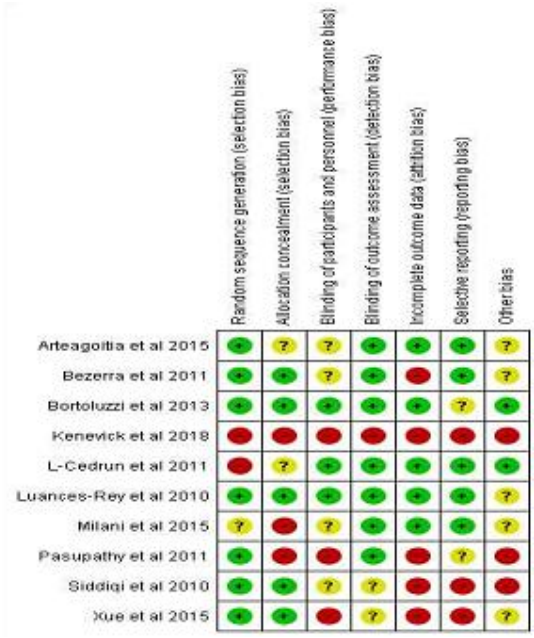

Fig 2: 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

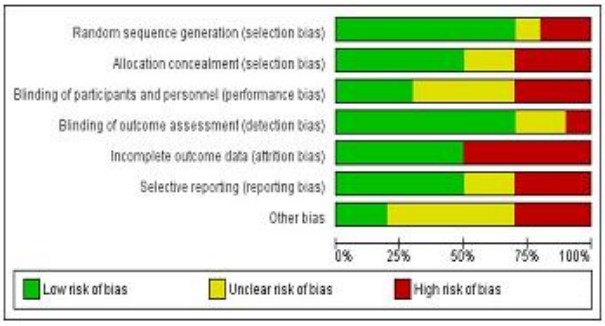

Fig 3: Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

These could be explained by the usage of amoxicillinin combination with clavulanic. Clavulanic acid is a beta lactamase inhibitor that has a strong bactericidal effect when used in combination with amoxicillin. Systemic circulation of the amoxicillin/clavulanic acid exhibits a good permeation and it reaches the antibacterial concentrations in bone, middle ear, peritoneum and synovial fluid [39] Amoxicillin + clavulanic acid had an overall (71.2/million prescriptions) and serious (51.4/million prescriptions) ADR rate >3 times that of amoxicillin. [40] The main adverse reactions are gastrointestinal, hepatobiliary and skin affections. Four studies described the prescription of 1 gr of amoxicillin 1 hour before. [30, 31, 33, 36]. The percentage of infection cases with amoxicillin were between 2.1- 10%. These studies proved that the use of amoxicillin is a safe option in antimicrobial prophylaxis as a non-adverse outcome were registered [40, 41]. As a last type of dosage, Xue et al. [37] prescribed a 500mg of amoxicillin 1 hour before and the alternative drug used in cases of allergic patients is a single dose of clindamycin 300mg. Clindamycin had the highest fatal adverse reactions rate (2.9/million prescriptions). [40] Nearly all fatal reactions were related to *Clostridiodes difficile* infection. Furthermore, most of the nonfatal clindamycin adverse reactions registered were pruritus and allergic rashes.

It should also be noted that gastrointestinal disturbances make for a significant proportion of the adverse reactions recorded for all antibiotics examined. Clindamycin had the highest rate of gastrointestinal disturbance reactions reported, followed by clarithromycin, metronidazole, and erythromycin and the most frequent gastrointestinal disturbances reported for all antibiotics were nausea and diarrhea [41].

Limitations

This study has several limitations. Not all studies evaluated the same symptoms therefore it was not possible to compare some of the variables like alveolitis, osteitis and trismus.

Several studies like Milani *et al* and Bortoluzzi *et al* have a small study sample, therefore it not possible to extrapolate the results of the reported cases.

Several studies that indicated a low percentage of infections also administered postoperative antibiotic therapy [29, 30,

35, 36, 37, 38] therefore, it was not possible to associate the possible benefits of antibiotic therapy to the preoperative dosage or postoperative dosage. Regarding this issue, authors like Milani *et al* and Xue *et al*, included in their studies a group with non-prophylactic antibiotics and only postoperative antibiotics were used. Their results indicated that the use of preoperative antibiotic prophylaxis is not effective in the prevention of local infections in oral surgery.

There is one study that suggests that the use of a combination of antibiotic and corticosteroid [34] may prevent further postoperative complications as inflammation, edema and pain.

It is worth notice that Kennevick *et al* [38] didn´t report any postoperative infections in a study group of 400 patients, neither this paper accomplishes any of the Cochrane criteria for risk of bias. Therefore, the result is somehow questionable.

5. CONCLUSION

The usage of prophylactic antibiotic therapy in oral surgery is not effective and doesn´t improve the overall results of the surgical intervention.

In our opinion in patients without systemic disease, the protocol for oral surgery should avoid the usage of prophylactic antibiotic therapy lowering the cost of the surgery and limiting the economic burden to the society. Furthermore, studies are needed in order to assets the effectiveness of preoperative and postoperative antimicrobial therapies in oral surgery.

6. REFERENCES

1. Bascones A, Aguirre JM, Bermejo A, Blanco A, Gay-Escoda C, González-Moles MA, GutiérrezPérez JL, Jiménez Soriano Y, LiébabaUreña J, López-Marcos JF, Maestre Vera JR, Perea Pérez EJ, Prieto Prieto J, de Vicente Rodríguez JC. Documento de consenso sobre el tratamiento antimicrobiano de las infecciones bacterianas odontogénicas. Med Oral Patol Oral Cir Bucal 2004; 9:363-76.
2. Altemeier WA, Burke JP, Pruitt BA, Sandusky WR. Manual of control on infection in surgical patients. JB Lippincott Co., Philadelphia 1976.
3. Martínez Lacasa J, Jiménez J, Ferrás VA, García- Rey C, Bosom M, Solá-Morales O, Aguilar L, Garau J. A double blind, placebo-controlled, randosmised, comparative phase III clinical trial of pharmacokinetically enhanced amoxicillin/ clavulanate 2000/125, as prophylaxis or as treatment versus placebo for infectious and inflammatory morbidity after third mandibula removal. Program and Abstracts of the 43rd InterScience Conference on Antimicrobial Agents and Chemotherapy, Chicago 2003. American SocietyforMicrobiology, Washington, DC.
4. Brook I, Lewis M A, Sandor G K *et al*. Clindamycin in dentistry: more than just effective prophylaxis for endocarditis? Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005; 100: 550-58.
5. Addy L D, Martin M V. Clindamycin and dentistry. *Br Dent J* 2005; 199: 23-26.
6. Mueller S C, Henkel K, Neumann J *et al.* Perioperative antibiotic prophylaxis in maxillofacial surgery: penetration of clindamycin into various tissues.J Craniomaxillofac Surg 1999; 27: 172-176.
7. Pear SZ, Williamson TH, Bettin KM, Gerding DN, Galgiani JN. Decrease in nosocomial Clostridium difficile-associated diarrhea by restricting clindamycin use. Ann Intern Med 1994; 120:272-7.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336–41.
9. Harbour R, Lowe G, Twaddle S. Scottish Intercollegiate Guidelines Network; the first 15 years (1993–2008). J R Coll Physicians Edinb 2011;41:163–8
10. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods Group; Cochrane Statistical Methods Group: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011, 343.
11. Chardin, H., Yasukawa, K., Nouacer, N, Reduced susceptibility to amoxicillin of oral streptococci following amoxicillin exposure. J Med Microbiol. 2009; 58:1092–7.
12. Al-Nawas, B., Walter, C., Morbach, T., Seitner, N., Siegel, E., Maeurer, M., Krummenauer, F. Clinical and microbiological efficacy of moxifloxacin versus amoxicillin/clavulanic acid in severe odontogenic abscesses: a pilot study.Eur. J. Clin. Microbiol. Infect. Dis, 2008. *28*: 75–82.
13. Matijevic, S., Lazic, Z., Kuljic-Kapulica, N., & Nonkovic, Z. Empirical antimicrobial therapy of acute dentoalveolar abscess. Vojnosanitetski pregled 2009; 66: 544–550.
14. Cachovan G, Boger RH, Giersdorf I, Hallier O, Streichert T, Haddad M, Platzer U, Schon G, Wegscheider K, Sobottka I. Comparative efficacy and safety of moxifloxacin and clindamycin in the treatment of odontogenic abscesses and inflammatory infiltrates: a phase II, double-blind, randomized trial. Antimicrob. Agents Chemother 2011; 55:1142–7.
15. Sisalli U., Lalli C., Cerone L., Maida S., Manzoli L., Serra E., Dolci M. Amoxicillin and clavulanic acid vs. ceftazidime in the surgical extraction of impacted third molar: a comparative study. Int J Immunopathol Pharmacol 2012;25:771–4
16. Sobottka I, Wegscheider K, Balzer L, Böger RH, Hallier O, Giersdorf I et al. Microbiological analysis of a prospective, randomized, double- blind trial comparing moxifloxacin and clindamycin in the treatment of

odontogenic infiltrates and abscesses. Antimicrob Agents Chemother 2012;56:2565-9.
17. Figueiredo R, Valmaseda-Castellon E, Formoso-Senande MF, Berini-Aytes L, Gay-Escoda C. Delayed-onset infections after impacted lower third molar extraction: involved bacteria and sensitivity pro les to commonly used antibiotics. Oral Surg Oral Med Oral Path Oral Radiol 2012;114:43-8.
18. Lee JY, Do HS, Lim JH, Jang HS, Rim JS, Kwon JJ, et al. Correlation of antibiotic prophylaxis and di culty of extraction with postoperative in ammatory complications in the lower third molar surgery. Br J Oral Maxillofac Surg. 2014;52:54-7.
19. Iglesias-Martín F, García-Perla-García A, Yañez-Vico R, Aced- Jiménez E, Arjona-Gerveno E, González-Padilla JD, Gutierrez- Pérez JL, Torres-Lagares D. Comparative trial betweenthe use ofamoxicillin and amoxicillinclavulanate in theremovalofthirdmolars. Med Oral Patol Oral Cir Bucal. 2014;19:612-5.
20. Igoumenakis D, Giannakopoulos NN, Parara E, Mourouzis C, Rallis G. Effect of Causative Tooth Extraction on Clinical and Biological Parameters of Odontogenic Infection: A Prospective Clinical Trial. J Oral Maxillofac Surg 2015; 73:1254–58.
21. Zirk M, Buller J, Goeddertz P, Rothamel D, Dreiseidler, T, Zöller J E, & Kreppel M. Empiric systemic antibiotics for hospitalized patients with severe odontogenic infections. J Cranio maxillofac Surg. 2016;44:1081-8.
22. Bali R, Sharma P, & Gaba S. Use of metronidazole as part of an empirical antibiotic regimen after incision and drainage of infections of the odontogenic spaces. Br J Oral Maxillofac Surg 2015;53:18-22
23. Braimah R O, Ndukwe K C, Owotade J F, Aregbesola S B. Impact of oral antibiotics on health-related quality of life after mandibular third molar surgery: An observational study. Niger J Clin Pract. 2017, 20, 1189–94.
24. Adde CA, Soares M S, Romano M M, Carnaval T G, Sampaio R M, Aldarvis F P, Federico L R. Clinical and surgical evaluation of the indication of postoperative antibiotic prescription in third molar surgery. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 2012, 114, 26–31.
25. Duvall N B, Fisher T D, Hensley D, Hancock R H, Vandewalle K S. The comparative efficacy of 0.12%chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteremia during third molarextractions: a prospective, blind, randomized clinical trial. Oral Surg. Oral Med. Oral Pathol. Oral Radiol.Endod. 2013; 115: 752–63
26. Crincoli V, Di Comite M, Di Bisceglie, M.B; Petruzzi, M Fatone L, De Biase C, Tecco S, Festa, F. Whichroute of antibiotic administration should be used for third molar surgery? A split-mouth study to compareintramuscular and oral intake. Clin. Ter**.** 2014, 165, 12–16.
27. Monaco, G.; Tavernese, L.; Agostini, R.; Marchetti, C. Evaluation of antibiotic prophylaxis in reducingpostoperative infection after mandibular third molar extraction in young patients. J. Oral Maxillofac. Surg. 2009; 67: 1467–72.
28. Kumari S, Mohanty S, Sharma P, Dabas J, Kohli S, Diana C:Is the routine practice of antibiotic prescription and microbial culture and antibiotic sensitivity testing justified in primary maxillofacial space infection patients? A prospective, randomizedclinicalstudy.. J Craniomaxillofac Surg 2018; 46: 446-52.
29. Luaces-Rey R, Arenaz-Bua J, Lopez-Cedrun-Cembranos JL, Martinez-Roca C, Pertega-Diaz S, Sironvalle-Soliva S. Efficacy and safety comparison of two amoxicillin administration schedules after third molar removal. A randomized, double-blind and controlled clinical trial. Med Oral Patol Oral Cir Bucal. 2010;15;633–8.
30. Siddiqi A, Morkel JA, Zafar S. Antibiotic prophylaxis in third molar surgery: A randomized double-blind placebo-controlled clinical trial using split-mouth technique. Int J Oral MaxillofacSurg. 2010; 39:107–114.
31. Bezerra TP, Studart-Soares EC, Scaparo HC, Pita-Neto IC, Batista SH, Fonteles CS. Prophylaxis versus placebo treatment for infective and inflammatory complications of surgical third molar removal: a split-mouth, double-blind, controlled, clinical trial with amoxicillin (500 mg) J Oral Maxillofac Surg. 2011;69:333–9.
32. Lopez-Cedrún J, Pijoan J, Fernández S, Santamaria J, Hernandez G. Efficacy of amoxicillin treatment in preventing postoperative complications in patients undergoing third molar surgery: a prospective, randomized, double-blind controlled study. J Oral Maxillofac Surg 2011;69:5–14.
33. Pasupathy S, Alexander M. Antibiotic prophylaxis in third molar surgery. J Craniofac Surg. 2011;22(2):551–553
34. Bortoluzzi MC, Capella DL, Barbieri T, Pagliarini M, Cavalieri T, Manfro R. A single dose of amoxicillin and dexamethasone for prevention of postoperative complications in third molar surgery: a randomized, double-blind, placebo controlled clinical trial. J Clin Med Res. 2013;5:26-33.
35. Arteagoitia I, Ramos E, Santamaria G, Barbier L, Alvarez J, Santamaria J. Amoxicillin/ clavulanic acid 2000/125 mg to prevent complications due to infection following completely bone-impacted lower third molar removal: a clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:8–16.
36. Milani B A, Bauer H C, Sampaio-Filho H, Horliana A C, Perez F E, Tortamano I P, Jorge W A. Antibiotic therapy in fully impacted lower third molar surgery:

randomized three-arm, double-blind, controlled trial. Oral Maxillofac. Surg. 2015; *19*: 341–346.
37. Xue P, Wang J, Wu B, Ma Y, Wu F, Hou R. Eficacy 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.
38. Knežević A,Knežević D, GranićM,KunaT, Grgić N, Gabrić D. Does A Single Dose of Systemic Antibiotic Prevent Postoperative Inflammatory Complications After Lower Third Molar Surgery? A Randomized Controlled Trial. RJPBCS. 2018, 9: 1223.
39. Esen, A. The Effects of Amoxicillin with Or Without Clavulanic Acid on The Postoperative Complaints After Third Molar Surgery: A Retrospective Chart Analysis. J Istanb Univ Fac Dent, 2017, 51; 2.
40. Thornhill M, Dayer M, Durkin M, Lockhart P, Baddour L. Risk of Adverse Reactions to Oral Antibiotics Prescribed by Dentists. J Dent Res 2019: *98*: 1081–7.
41. Baddour L M, Dayer M J, Thornhill M H. Fluoroquinolone use and associated adverse drug events in England. J Infect 2019; 78: 249-59.

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