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Review

Antibiotic Prophylaxis in the Prevention of Postoperative Infections in Mandibular Third Molar Extractions: Systematic Review and Meta-Analysis

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Featured Application: Short pre-surgical antibiotic prophylaxis is effective and recommended for prevention of surgical wound infection after extraction of a mandibular third molar.

Abstract: Background: This systematic review and meta-analysis aims to evaluate the effectiveness of antibiotic prophylaxis in the prevention of surgical wound infection (SWI) following mandibular third molar extraction. Methods: A systematic search on electronic databases and a manual search on paper journals was carried out. Two independent reviewers selected the studies. The onset of SWI was used as the main outcome. The data from the studies were analyzed, both with the fixed and the random models, according to the type of antibiotic and the method of administration; a further stratification was adopted, if possible, based on surgical difficulty. The risk of bias and heterogeneity were evaluated. Results: 15 studies were included. Antibiotic prophylaxis, especially in pre-surgical administration and in case of osteotomy, is effective in the prevention of SWI in case of mandibular third molar extraction. Post-surgical administration of prophylaxis, although effective, does not seem to be fully supported by the literature. Pre- and post-surgical prophylaxis did not demonstrate superiority compared to pre-surgical administration alone. Conclusions: Antibiotic prophylaxis is effective in reducing SWI after third molar extraction; pre-surgical administration, minimizing antibiotics administration, allows one to reduce complications related to antibiotic and risk of onset of antibiotic resistance.

Keywords: third molar surgery; mandible; surgical wound infection; antibiotic prophylaxis; humans; systematic review; meta-analysis

Citation: Lupi, S.M.; Olivieri, G.; Landini, J.; Ferrigno, A.; Richelmi, P.; Todaro, C.; Rodriguez y Baena, R. Antibiotic Prophylaxis in the Prevention of Postoperative Infections in Mandibular Third Molar Extractions: Systematic Review and Meta-Analysis. *Appl. Sci.* **2021**, *11*, 9449. https://doi.org/10.3390/app11209449

Academic Editor: Bruno Chrcanovic

Received: 8 September 2021
Accepted: 7 October 2021
Published: 12 October 2021

1. Introduction

According to different authors, third molar extraction is one of the most common surgeries carried out in dentistry [1]. The main reasons of its extraction are pain, infection, unfavorable position, need of space for orthodontic treatment or second molar decay caused by this element [2]. Its extraction often leads to post-operative infections or other complications [3]. Frequently, after surgery, patients accuse pain and there could also be fever, swelling, trismus, dysphagia, presence of dry sockets, lymphadenopathy, abscesses and infections [2].

The third molar is usually totally or partially impacted and it could have different inclinations, making its extraction more difficult than others. Obviously, the more the tooth is under the bone and/or inside the rising branch of the mandible (respectively

Class III and Class C of Pell & Gregory Classification, 1933 [4]), the more difficult the extraction will be for the dentist and more disposed to complications. Extractions are considered complicated when the operator is forced to use burs to remove bone and, sometimes, also to cut the tooth in sections. Different authors find that osteotomy leads to post-operative infection more frequently than a simple extraction does [5]. Many studies suggest giving antibiotic therapy in order to avoid or limit the recurrence of infection after third molar extraction. Different antibiotics could be used, but the most common is amoxicillin and clavulanic acid [5]. This one is particularly effective and generally well tolerated. Otherwise, clindamycin, doxycycline, erythromycin, tinidazole, metronidazole and others can be used. An antibiotic could cause different side effects, such as headache, gastric pain, nausea, diarrhea, rash and vomiting, up to anaphylactic reactions [6]. These adverse events are mostly mild or moderate, but it is possible that patients could need to stop antibiotic therapy because of severe side effects. These events, together with antibiotic resistance, are the major issue related to this kind of medicines [1]. Researchers must analyze benefit/risk ratio of antibiotic therapy, in order to understand when it can be used.

Different articles have been written about this topic in the last years. In the literature, it is considered a controversial issue even nowadays.

Menon's review, written in 2019, analyzed eleven different articles and concluded that antibiotic, especially amoxicillin with clavulanic acid one, is effective in reducing post-operative complications after third molar extraction [7]. Nevertheless, the author suggests carefully considering the possible administration of antibiotic therapy after this surgery because of the effect of this type of medicine. More specifically, antibiotic destroys lots of bacteria, also the physiological ones, and could lead to antibiotic resistance. Similar results were obtained by other reviews, such as Ren [1], Conaty [8], Marcussen [9]. In particular, this last one considers a single dose of amoxicillin given before third molar extraction when osteotomy is needed. This review considers the quality of the articles included in order to limit the risk of bias.

Another review from the literature [10] analyzed antibiotic therapy outcomes, including any type of antibiotic and different doses, frequency and pattern of delivery. The author established that administrating any kind of antibiotic is helpful in reducing the risk of infection after third molar extraction. Therefore, it seems that not only amoxicillin is effective in this purpose.

On the other hand, another review [11] concluded that amoxicillin has no potential in reducing the risk of post-operative infection, either given pre-surgically or post-surgically. A possible criticism to this work is the extremely small number of articles included. Because of that, it is possible that results are not completely reliable.

In addition, Martin [12] wrote an article about the use of antibiotic prophylaxis after third molar surgery and he affirms there is no reason in favor of prescribing this medicine. It is necessary to point out that this article is an author's opinion and it is not a study derived from the analysis of other reviews; consequently, there are no objective results.

A well written review was made by Chugh [6], in which thirteen studies were analyzed. The conclusion of this work is that antibiotic therapy can be considered a useful enforcement in avoiding infections after third molar extraction. This article can be considered reliable because it also analyzed the level of the quality of each paper, number of quotations and journal impact factor.

Our review analyses literature about antibiotic prescription after third molar extraction, both as prophylaxis and as long therapy. More specifically, we have considered the frequency of infections in antibiotic and placebo groups and the possible correlation between osteotomy, odontotomy and infections. This review aims to find reliable results that can be useful for the dentist in choosing the correct therapy (or absence of therapy) after third molar extraction. This systematic review and meta-analysis aimed to evaluate the effectiveness of antibiotic prophylaxis, compared to the absence of prophylaxis/placebo, in the prevention of post-operative infections of the surgical site following the extraction of a mandibular third molar.

2. Materials and Methods

To identify all articles of interest for this review and meta-analysis, a systematic search of literature was conducted in PubMed, Medline, Scopus, Web of Sciences. The search string is shown in Table 1. The following search terms were used: "Third molar surgery", "mandible", "surgical wound infection", "Postoperative infection", "antibiotic prophylaxis", "humans", "randomized clinical trial", "RCT". The search has been updated up to July 2021. To find out any studies not identified by the electronic search, references of the included articles were evaluated, and numerous paper journals were manually searched.

Table 1. Pubmed/medline search string.

(randomized controlled trial [PT] OR controlled clinical trial [PT] OR randomized controlled trials [MH] OR random allocation [MH] OR double-blind method [MH] OR single-blind method [MH] OR clinical trial [PT] OR clinical trials [MH] OR ("clinical trial" [TW]) OR ((singl* [TW] OR doubl* [TW] OR trebl* [TW] OR tripl* [TW]) AND (mask* [TW] OR blind* [TW])) OR (placebos [MH] OR placebo* [TW] OR random* [TW] OR research design [MH:noexp]) NOT (animals [MH] NOT humans [MH])) AND (((Molar, Third/surgery [MH]) OR (*Tooth Extraction/adverse effects [MH])) AND ((Amoxicillin/therapeutic use [MH]) OR (Anti-Bacterial Agents/therapeutic use [MH]) OR (Antibiotic Prophylaxis/*utilization [MH]) OR (Endocarditis, Bacterial/prevention and control [MH]) OR (Pain, Postoperative/prevention and control [MH]) OR (Surgical Wound Infection/prevention and control [MH]) OR (Surgical Wound Infection/prevention and control [MH])))

In the present work our aim was to summarize the available evidence on antibiotic prophylaxis efficacy in preventing surgical wound infections in patients undergoing mandibular third molar extraction by conducting a meta-analysis. To achieve this, the following PICO format was applied: extraction of a mandibular third molar (Population); administration of antibiotic prophylaxis (Intervention); placebo/no administration (Comparison); appearance of signs of surgical wound infection (Outcome).

The exclusion criteria were: systematic reviews, meta-analyses, case reports, case series, letters to the editor, expert opinions, retrospective studies, prospective non-randomized studies, studies in which it was not possible to specifically identify data concerning mandibular third molars (e.g., studies on generic extraction of impacted teeth or extraction of mandibular and maxillary third molars), absence of placebo, articles in other languages than English, French, Spanish, and German. No limitations were applied for publication date. All articles were review initially by 2 experts (GO and JL). In case of discrepancies, these were resolved by SML.

2.1. Evidence Quality Evaluation and Data Extraction

All the articles included in the final selection were submitted to a qualitative analysis. In order to measure the likelihood of bias of these randomized clinical trials, we chose the final version of Jadad's instrument [13]. The scale ranges from 0 to 3 points at each article, with possible extra plus or minus points, based on the answers to the following questions: i. Is the study randomized? ii. Is it a double blinded study? iii. Does the article explain withdrawals and dropouts, with a specific explanation of the reasons? For each affirmative answer, the article obtains one point; for each negative answer, the article does not acquire any points. Moreover, it is possible to gain an extra point if the randomization sequence is well described and it results appropriate (using a table of random numbers or computer generate numbers) and/or if the double blind is also well described and it is appropriate (i.e., identical placebo). In addition, it is possible to remove points whether the randomization is inappropriate (giving sequential numbers or giving numbers on the base of the date of birth) and/or if the double blind is inappropriate (i.e., absence of identical placebo). At the end, a number from -2 to 5 is assigned to each article.

The data were extracted from the articles by an operator (CT) and recorded on a spreadsheet. The data extracted were: authors, year of publication, country, sample size, groups size, number of events in the test group and in the control group, osteotomy, odontotomy, randomization, double blind, explanation for withdrawals.

2.2. Meta-Analysis

The results of the meta-analysis were expressed as Relative Risk (RR) since the studies included in the meta-analysis were only RCTs and this descriptor is easier to interpret.

The analysis was conducted using both fixed and random models to evaluate whether the conclusions could be affected by the chosen model [14].

To evaluate the heterogeneity of the studies, the $\tau 2$ estimated with the DerSimonian-Laird method and I2 were used. Heterogeneity was considered mild for values <30%, moderate for values between 30% and 50% and notable for values >50% [15,16].

Because statistical tests of heterogeneity have low power and to avoid type II errors, a significance level of 0.10 instead of the more traditional level of 0.05 was chosen [17,18].

The presence of significant heterogeneity was discussed to possibly identify a source of clinical heterogenicity [14].

R software was used for the statistical analysis of the results and the execution of the meta-analysis [19].

3. Results

The literature search initially identified 380 articles; 338 of these were discarded by reading the title and abstract because they were irrelevant (Figure 1). Among the remaining 42 articles, 27 were discarded after reading the complete article for the reasons listed in Table S1 (see Supplementary material). Fifteen articles remained and were included in this systematic review of literature and meta-analysis. The characteristics of the articles used for the meta-analysis are listed in Table 2.

The articles included in the meta-analysis were evaluated for the risk of bias (Table 3).

The results of the meta-analysis are reported in Table 4.

The following comparisons are not reported in Table 4 because it was not possible to conduct them due to the insufficient number of studies: 1. non-penicillin antibiotics vs. placebo in the surgery requiring osteotomy subgroup for all the modality of administration; 2. all comparison including surgery requiring odontotomy and post-surgery administration of prophylaxis; 3. penicillin vs. non penicillin antibiotics in pre-, pre- and post-, and post-surgery administration modality.

Table 2. Characteristics of included studies.

Study	Country	Total Sample Size	Comparisons	Conclusions
Arteagoitia et al., 2015 [20]	Spain	118	- 2000/125 mg A/aC 2 h before surgery + 2000/125 mg A/aC BID × 4 days - Placebo	Insufficient evidence to recommend routine use of this antibiotic treatment
Arteagoitia et al., 2005 [21]	Spain	490	- 1500/375 mg A/aC TID after surgery × 4 days - Placebo	A/aC is efficacious in reducing the incidence of inflammatory complications following third molar extraction but should not be prescribed in all cases
Bulut et al., 2001 [22]	Turkey	60	- 1 g A 1 h before surgery + 1 g A BID × 4 days after surgery - Placebo	The results revealed no statistically significant difference between treated and control patients in terms of incidence of postoperative infection.

Table 2. *Cont.*

Study	Country	Total Sample Size	Comparisons	Conclusions
Bystedt et al. 1980 [23]	Sweden	140	- 750 mg azidocillin 1 h before surgery + 1500 mg azidocillin BID during 7 days after surgery - 500 mg E o 300 mg clindamycin 90 min before surgery + 1000 mg erythromycin o 600 mg clindamycin QID during 7 days after surgery - 200 mg doxycycline 3 h before surgery + 100 mg doxycycline daily during 7 days after surgery - Placebo	Systemically administered antibiotics offered only slight advantages in routine operations of impacted third mandibular molars, but could decrease the rate of infections after traumatic operations
Curran et al. 1974 [24]	Canada	133	- IM penicillin G 1 h before + 1 g OS penicillin G QID during 4 days - 2. No antibiotics	Use of prophylactic antibiotics in third molar surgery is unnecessary unless specific systemic factors are present
Kaczmarzyk et al., 2007 [25]	Poland	86	- 600 mg clindamycin 1 h before surgery + placebo TID during 5 days after surgery - 600 mg clindamycin 1 h before surgery + 900 mg clindamycin TID during 5 days after surgery - Placebo 1 h before surgery + placebo TID during 5 days after surgery	Clindamycin applied in a single pre-surgical dose of 600 mg with or without subsequent 5-day therapy does not demonstrate efficacy in prophylaxis for postoperative inflammatory complications
Lacasa et al., 2007 [26]	Spain	222	- 2000/125 mg A/aC before surgery + placebo during 5 days after surgery - Placebo before surgery + 2000/125 mg A/aC during 5 days after surgery - Placebo before surgery + placebo during 5 days after surgery	Prophylaxis was beneficial in simpler procedures and may be suitable in cases where ostectomy is not performed.
Lopez Cedrun et al., 2011 [27]	Spain	123	- 2 g A 2 h before surgery + placebo during 5 days after surgery - Placebo before surgery + 1500 mg A TID during 5 days after surgery - Placebo before surgery + placebo during 5 days after surgery	Amoxicillin administered pre- or postoperatively demonstrated greater efficacy than placebo in preventing postoperative complications in patients undergoing third molar surgery. The best results were obtained using the postoperative protocol.

Table 2. *Cont.*

Study	Country	Total Sample Size	Comparisons	Conclusions
Milani et al., 2015 [28]	Brasil	80	- 1 g A 1 h before surgery + 1500 mg A TID during 7 days after surgery - 1 g A 1 h before surgery + placebo TID during 7 days after surgery - Placebo 1 h before surgery + placebo TID during 7 days after surgery	No advantage in the administration of antibiotics in healthy patients undergoing extraction of fully impacted lower third molars with a controlled aseptic chain
Mitchell 1986 [29]	United Kingdom	89	- 2 g tinidazole prima - Placebo	Antibiotic prophylaxis is effective in preventing complications and infections following the extraction of included mandibular third molars
Monaco et al., 2009 [30]	Italy	59	- 2 g A 1 h before surgery - No antibiotics	Significative difference between patients receiving preoperative amoxicillin and the control group in wound infections and consumption of analgesics
Pasupathy & Alexander 2011 [31]	India	89	- Placebo - 1 g A 1 h before surgery - 800 mg metronidazole 1 h before surgery	No statistically significant difference between the groups
Poeschl et al., 2004 [32]	Austria	528	- 2 g A/aC BID during 5 days - 900 mg clindamycin TID during 5 days - No antibiotics	Postoperative oral prophylactic antibiotic treatment after the removal of lower third molars does not contribute to a better wound healing, less pain, or increased mouth opening and could not prevent the cases of inflammatory problems after surgery, respectively, and therefore it is not recommended for routinary use
Sekhar et al., 2001 [33]	India	125	- Placebo - 1000 mg metronidazole 1 h before surgery - 1200 mg metronidazole TID during 5 days after surgery	Antimicrobial prophylaxis does not seem to reduce morbidity after removal of lower third molars
Xue et al., 2015 [34]	China	384	- 500 mg A 1 h before + 1500 mg A TID during 3 days after surgery - Placebo	Prophylactic amoxicillin (or clindamycin) is not effective in the prevention of postoperative inflammatory complications after impacted mandibular third molars removal

A: amoxicillin; A/aC: amoxicillin + clavulanate.

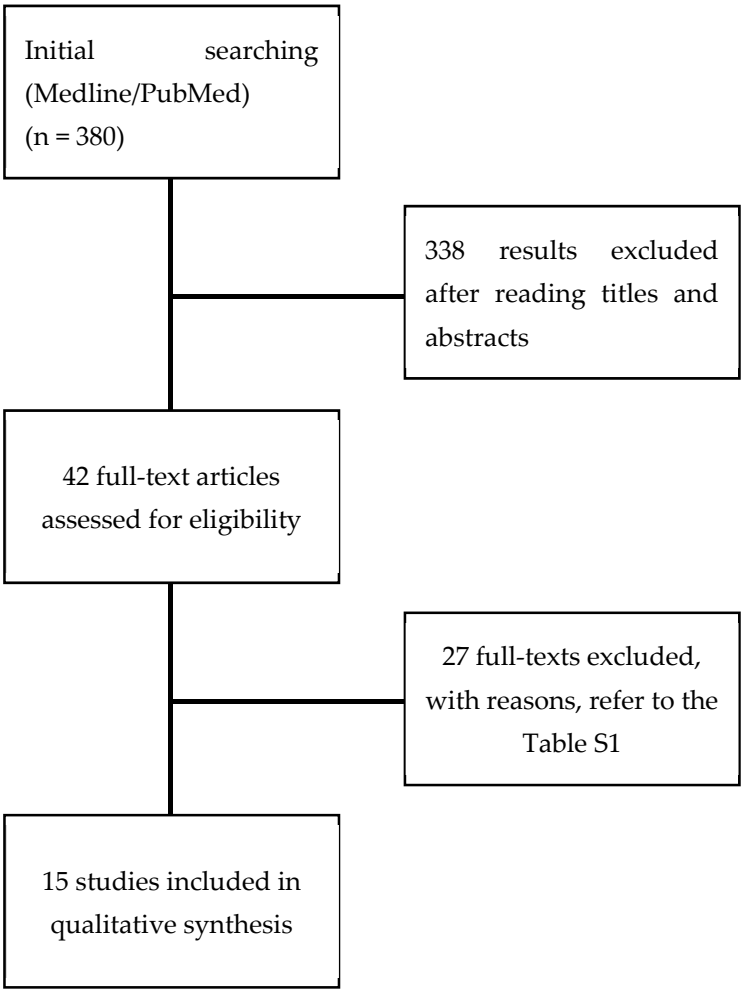

Figure 1. Diagram of the systematic review of literature.

Table 3. Risk of bias of included studies.

Study	Random Allocation	Double Blinded	Explanation for Withdrawals	JADAD Score
Arteagoitia et al., 2015 [20]	Yes	Yes	Yes	4
Arteagoitia et al., 2005 [21]	Yes	Yes	Yes	4
Bulut et al., 2001 [22]	Yes	Yes	No	2
Bystedt et al. 1980 [23]	Yes	Yes	No	2
Curran et al. 1974 [24]	Yes	Yes	Yes	2
Kaczmarzyk et al., 2007 [25]	Yes	Yes	Yes	4
Lacasa et al., 2007 [26]	Yes	Yes	Yes	4
Lopez Cedrun et al., 2011 [27]	Yes	Yes	Yes	3
Milani et al., 2015 [28]	Yes	Yes	Yes	4
Mitchell 1986 [29]	Yes	Yes	Yes	3
Monaco et al., 2009 [30]	Yes	No	No	1
Pasupathy & Alexander 2011 [31]	Yes	Yes	Yes	4
Poeschl et al., 2004 [32]	Yes	No	Yes	2
Sekhar et al., 2001 [33]	Yes	Yes	Yes	3
Xue et al., 2015 [34]	Yes	Yes	No	3

Table 4. Summary of meta-analysis results.

Comparison	N. Included Studies	N. Test	N. Control	N. Total	RR Fixed	p Fixed	RR Random	p Random	I^2	p	NNT
All methods of administration											
ATBs (overall) vs. placebo	15	1618	1108	2726	0.43 (0.32; 0.59)	<0.0001	0.40 [0.26; 0.63]	<0.0001	43%	0.04	15
Pre-surgery administration											
ATBs (overall) vs. placebo	8	356	296	652	0.29 (0.16; 0.52)	<0.0001	0.29 [0.16; 0.52]	<0.0001	0%	0.47	9
ATBs (penicillin) vs. placebo	5	207	191	398	0.39 (0.18; 0.85)	0.0164	0.40 [0.17; 0.94]	0.0421	10%	0.35	13
ATBs (others) vs. placebo	4	149	134	283	0.23 (0.10; 0.53)	0.0005	0.23 [0.10; 0.53]	0.0005	0%	0.52	6
Pre- and post-surgery administration											
ATBs (overall) vs. placebo	7	484	456	940	0.56 (0.34; 0.94)	0.0265	0.56 [0.34; 0.94]	0.0265	0%	0.68	28
ATBs (penicillin) vs. placebo	4	312	300	612	0.72 (0.33; 1.54)	0.3935	0.72 [0.33; 1.54]	0.3935	0%	0.77	68
ATBs (others) vs. placebo	3	172	156	328	0.47 (0.24; 0.92)	0.0277	0.47 [0.23; 0.97]	0.0404	10%	0.33	13
Post-surgery administration											
ATBs (overall) vs. placebo	4	778	552	1330	0.46 (0.29; 0.74)	0.0012	0.26 [0.07; 0.94]	0.0393	79%	<0.01	15
ATBs (penicillin) vs. placebo	4	551	518	1069	0.40 (0.24; 0.66)	0.0004	0.26 [0.08; 0.89]	0.0314	75%	<0.01	12
ATBs (others) vs. placebo	1	227	206	433	0.96 (0.48; 1.89)	0.8964	0.96 [0.48; 1.89]	0.8964	NA	NA	148
Subgroup analysis: Surgery requiring osteotomy—All methods of administration											
ATBs (overall) vs. placebo	11	1032	731	1763	0.54 (0.38; 0.76)	0.0003	0.50 [0.32; 0.77]	0.0015	28%	0.18	19
Subgroup analysis: Surgery requiring osteotomy—Pre-surgery administration											
ATBs (overall) vs. placebo	5	156	150	306	0.27 (0.13; 0.57)	0.0005	0.27 [0.13; 0.57]	0.0005	0%	0.41	6
ATBs (penicillin) vs. placebo	3	96	87	183	0.35 (0.12; 1.07)	0.0650	0.43 [0.09; 2.14]	0.3042	44%	0.17	10
ATBs (others) vs. placebo	2	60	63	123	0.22 (0.08; 0.59)	0.0028	0.22 [0.08; 0.59]	0.0028	0%	1.00	4
Subgroup analysis: Surgery requiring osteotomy—Pre- and post-surgery administration											
ATBs (overall) vs. placebo	7	484	456	940	0.56 (0.34; 0.94)	0.0265	0.56 [0.34; 0.94]	0.0265	0%	0.68	28
ATBs (penicillin) vs. placebo	4	312	300	612	0.72 (0.33; 1.54)	0.3935	0.72 [0.33; 1.54]	0.3935	0%	0.77	68
ATBs (others) vs. placebo	3	172	156	328	0.47 (0.24; 0.92)	0.0277	0.47 [0.23; 0.97]	0.0404	10%	0.33	13

Table 4. *Cont.*

Comparison	N. Included Studies	N. Test	N. Control	N. Total	RR Fixed	p Fixed	RR Random	p Random	I^2	p	NNT
Subgroup analysis: Surgery requiring osteotomy—Post-surgery administration											
ATBs (overall) vs. placebo	2	392	212	604	0.76 (0.44; 1.32)	0.3268	0.53 [0.14; 2.11]	0.3700	69%	0.07	26
ATBs (penicillin) vs. placebo	2	212	212	424	0.70 (0.37; 1.31)	0.2652	0.52 [0.14; 2.02]	0.3470	66%	0.09	24
Subgroup analysis: Surgery requiring odontotomy—All methods of administration											
ATBs (overall) vs. placebo	5	404	326	730	0.54 (0.27; 1.10)	0.0894	0.54 [0.27; 1.10]	0.0894	0%	0.55	41
Subgroup analysis: Surgery requiring odontotomy—Pre-surgery administration											
ATBs (overall) vs. placebo	3	122	76	198	0.45 (0.13; 1.52)	0.1990	0.51 [0.10; 2.45]	0.3978	36%	0.21	23
ATBs (penicillin) vs. placebo	3	93	76	169	0.62 (0.19; 2.10)	0.4459	0.66 [0.15; 2.95]	0.5901	30%	0.24	36
Subgroup analysis: Surgery requiring odontotomy—Pre- and post-surgery administration											
ATBs (overall) vs. placebo	3	282	270	552	0.67 (0.29; 1.55)	0.3505	0.67 [0.29; 1.55]	0.3505	0%	0.62	62
ATBs (penicillin) vs. placebo	3	282	270	552	0.67 (0.29; 1.55)	0.3505	0.67 [0.29; 1.55]	0.3505	0%	0.62	62
Subgroup analysis: Penicillin antibiotics vs. *non-penicillin antibiotics—All methods of administration*											
ATBs (penicillin) vs. ATBs (others)	2	207	209	416	1.04 (0.52; 2.04)	0.9186	1.06 [0.49; 2.26]	0.8881	3%	0.31	181

ATBs (overall): all types of antibiotics; ATBs (penicillin): amoxicillin, amoxicillin and clavulanic acid; ATBs (others): non-penicillin antibiotics.

4. Discussion

First of all, it is important to highlight that the present review and meta-analysis evaluated the effectiveness of antibiotic prophylaxis in the prevention of infectious complications on the operative site only in case of mandibular third molar extraction. For the meta-analysis, all the data taken as a whole were first considered, and then, subgroup analysis was carried out in case it was possible to extrapolate the data. Therefore, the effectiveness of antibiotic prophylaxis was evaluated even in case of only pre-surgical administration, pre- and post-surgical administration, and only post-surgical administration. This choice was made due to the different possible methods of administration: on the one hand, for example, pre- or pre- and post-surgical administration as for endocarditis prophylaxis; on the other hand, a reasonable clinical approach could be to administer antibiotic prophylaxis only after the completion of the surgery in case of difficult extraction, according to the judgment of the oral surgeon.

Furthermore, an initial evaluation was carried out regarding all types of antibiotics, and then, if possible, the literature data were stratified according to the type of antibiotic administered: only amoxicillin (with clavulanic acid) and only other antibiotics that were not penicillin. This choice was made to assess whether there was a benefit of one group of antibiotics over the others. In fact, amoxicillin is considered the most suitable broad-spectrum antibiotic for antibiotic prophylaxis, also for the prophylaxis of secondary infections such as bacterial endocarditis.

In addition, when possible, an analysis of data regarding ostectomy or odontotomy interventions was carried out, considering these elements as a risk factor linked to the use of high-speed drills and therefore to the possible formation of bone necrosis.

With regards to the qualitative analysis, each article was assessed using the final Jadad's instrument. Just one article was assigned with only 1 point (Monaco and Coll. [30]), four articles obtained 2 points (Bulut and Coll. [22], Bystedt and Coll. [23], Curran and Coll. [24], Poeschl and Coll. [32]), four articles gained 3 points (Lopez-Cedrun and Coll. [27], Mitchell and Coll. [29], Sekhar and Coll. [33], Xue and Coll. [34]), and six articles got 4 points (Arteagoitia and Coll. [20], Arteagoitia and Coll. [21], Kaczmarzyk and Coll. [25], Lacasa and Coll. [26], Milani and Coll. [28], Pasupathy & Alexander [31]).

The systematic review of the literature made it possible to identify 15 articles in order to carry out a meta-analysis, for a total of 2726 surgeries performed.

The meta-analysis carried out on all articles showed a benefit in the use of prophylactic antibiotics for the prevention of infectious complications with both the fixed and random analysis. This analysis entailed a moderate degree of heterogenicity, with a $p < 0.1$ (see Figure S1 in the Supplementary material section). This heterogenicity can be explained by the fact that all the methods of administration and all the drugs were considered together. Later in the discussion, it will be shown that some methods of recruitment have had a wider heterogenicity than others. The necessary number of patients to be treated to benefit from the administration of antibiotic prophylaxis, considering all the modalities and all types of antibiotics together, was equal to 15.

The meta-analysis of the data regarding antibiotic prophylaxis with all types of antibiotics, considering exclusively the pre-surgical administration, included 8 studies for a total of 652 surgeries performed (see Figure S2 in the Supplementary material section). In this case, the RR (0.29) significantly favored the prophylaxis both with the fixed and random models. Furthermore, the heterogenicity of the data was found to be zero and the number of patients to be treated to obtain a therapeutic benefit was equal to 9. Therefore, it is possible to state that literature homogeneously indicates a favorable effect in the pre-surgical administration of prophylactic antibiotics.

The efficacy of the exclusively pre-surgical administration of penicillin antibiotics was evaluated based on 5 studies, for a total of 398 surgeries performed (see Figure S3 in the Supplementary material section). This modality of prophylaxis showed a significant benefit, with a slight and insignificant heterogenicity, and an NNT equal to 13. Therefore, it can be stated that from the analysis of the literature, the results homogeneously indicate a favorable effect in favor of pre-surgical prophylactic penicillin antibiotics administration.

The meta-analysis of the data regarding pre-surgical prophylaxis with non-penicillin antibiotics, included 4 studies for a total of 283 surgeries (see Figure S4 in the Supplementary material section). The RR was significantly in favor of administering prophylaxis with both the fixed and random models, with an identical value. Furthermore, the heterogenicity of the data was found to be zero and the number of patients to be treated to obtain a therapeutic benefit was equal to 6. Therefore, it can be stated that from the analysis of the literature the results homogeneously indicate a favorable effect of pre-surgical administration of non-penicillin antibiotics.

Overall, therefore, the pre-surgical administration of antibiotics for the prophylaxis of surgical wound infections following the extraction of the mandibular third molar has a significant efficacy, homogeneously highlighted by the literature and with a significant clinical impact.

The pre- and post-surgical administration, considering all types of antibiotics, analyzed data from 7 different studies, for a total of 940 surgeries performed (see Figure S5 in the Supplementary material section). The results showed a significant benefit in favor of prophylaxis with a heterogenicity of zero but with an NNT of 28. The latter result is significantly higher than those relating to the exclusively pre-surgical modality. Pre- and post-surgical administration analysis, considering only amoxicillin, considered the data from 4 studies, for a total of 612 surgeries (see Figure S6 in the Supplementary material section). The results indicated a significant benefit in favor of prophylaxis with zero heterogenicity, but NNT was 68. The latter result is significantly higher than those relating to the exclusively pre-surgical modality.

Pre- and post-surgical administration analysis, considering non-penicillin antibiotics only, considered the data from 3 studies, for a total of 328 surgeries (see Figure S7 in the Supplementary material section). The results showed a significant benefit in favor of prophylaxis with mild and insignificant heterogenicity; the NNT was equal to 13. The latter result is significantly higher than the one relating to the exclusively pre-surgical modality for the same antibiotic.

Overall, the pre- and post-surgical administration of prophylactic antibiotics has shown significant efficacy in the prevention of surgical site infections, shown in a consistent manner by the studies in the literature, but with a lower clinical impact than the exclusively pre-surgical administration.

Post-surgical administration analysis, considering all types of antibiotics, included the data from 4 studies, for a total of 1130 surgeries performed (see Figure S8 in the Supplementary material section). The results indicated a significant benefit in favor of prophylaxis but with a high heterogenicity (79%, $p < 0.01$); the NNT was equal to 15. Although the result is significantly in favor of antibiotic prophylaxis, the high heterogenicity indicates that the studies conducted show discordant results. Post-surgical administration, considering amoxicillin only, included the data of 4 studies, for a total of 1069 surgeries performed (see Figure S9 in the Supplementary material section). Even considering only the administration of amoxicillin in the postoperative modality, the results suggest a significant benefit in favor of prophylaxis but with a high heterogenicity (75%, $p < 0.01$) and an NNT equal to 12. In addition, in this analysis, although the result is significantly in favor of antibiotic prophylaxis, the high heterogenicity indicates that the studies conducted report discordant results.

Post-surgical administration analysis considering only non-penicillin antibiotics did not find a significant difference between prophylaxis and placebo; furthermore, this analysis was conducted on only two studies of which one did not report any postoperative infection and therefore it was not possible to evaluate its heterogenicity (see Figure S10 in the Supplementary material section).

Overall, administration in the post-surgical mode showed significant efficacy in the prevention of surgical site infections, but the studies in the literature did not show concordant results.

Overall, therefore, the prophylactic administration of antibiotics was found to be effective in the prevention of surgical site infections and, among the various modalities, the exclusively pre-surgical administration seems to be the one most supported by the literature. The analysis of the data in the literature allows us to state that pre- and post-surgical antibiotic prophylaxis is less effective than the exclusively pre-surgical modality. These data are in contrast with the logic, since a greater coverage with antibiotics should reduce the risk of developing a post-operative infection of the wound. One possible explanation is that in case of exclusively pre-surgical administration, the dose of antibiotic administered was double in most cases [26,27,30,33] and therefore, during the operation, the blood concentration of the antibiotic was greater.

Even though the analysis of the data in the literature concerning post-surgical administration alone indicates a benefit from antibiotic prophylaxis, it also shows a lower benefit than other possible methods of administration and also reveals that the results of the studies do not agree.

For an effective prophylaxis, the antimicrobial has to be delivered to the operative site before contamination occurs. Thus, the antimicrobial serum and tissue concentrations should exceed the minimum inhibitory concentration (MIC) for the potential infective agent, for the duration of the entire procedure [35]. An appropriate administration of prophylaxis, including the appropriate drug, dose, and timing of administration, is essential to reduce surgical wound infections (SWIs). For most procedures, continuation of antibiotic prophylaxis after surgery is not required; nonetheless, this is frequently not adhered to, resulting in additional costs, an increased risk of antimicrobial resistance and side-effects including acute kidney injury and Clostridioides difficile infection [36]. In fact, there is

growing evidence that postoperative antimicrobial administration is not necessary for most procedures [35,37–39].

However, if post-surgical administration was deemed necessary, the duration of the therapy should be less than 24 h, in order to avoid the insurgence of bacterial resistance [35]; as a general rule, avoiding unnecessary use of antibiotics helps in diminishing the occurrence of adverse effects and antibiotic resistance development [40].

Therefore, it is possible to state from the data in the literature that antibiotic prophylaxis for the prevention of surgical site infections is useful and should be administered pre-surgically.

In the present review, a meta-analysis was also carried out considering only data on surgeries for which the odontotomy or osteotomy was explicitly reported. This analysis was chosen on a clinical experience basis which indicates, in case of odontotomy or osteotomy, a greater trauma on soft and hard tissues and therefore a greater risk of infection [41].

Nevertheless, it was not possible to carry out an analysis on the surgeries that did not require odontotomy or osteotomy as it was not explicitly reported in the published studies.

Considering all types of antibiotics and all methods of administration in case of osteotomy, 11 studies were considered in a total of 1763 surgeries performed (see Figure S11, Supplementary material). In this case, the RR, significantly in favor of prophylaxis, was 0.54 with the fixed model and 0.50 with the random model. Furthermore, the heterogenicity of the data was found scarce and insignificant (28%, $p > 0.10$) and the number of patients to be treated to obtain a therapeutic benefit was equal to 19. Therefore, it is possible to state that from the analysis of the literature the results homogeneously indicate a favorable effect of the administration of prophylactic antibiotics in case of osteotomy.

The meta-analysis of the data regarding pre-surgical prophylaxis with all types of antibiotics in case of osteotomy, included 5 studies for a total of 306 surgeries performed (see Figure S12, Supplementary material). In this case, the RR, significantly in favor of prophylaxis, was 0.27 both with the fixed and random models. Furthermore, the heterogenicity of the data was found to be zero and the number of patients to be treated to obtain a therapeutic benefit was equal to 6. Therefore, it can be stated that the literature homogeneously indicates a favorable effect in favor of administration of pre-surgical prophylactic antibiotics in case of osteotomy.

The effectiveness of the pre-surgical administration of penicillin antibiotics in case of osteotomy was evaluated based on 3 studies, for a total of 183 surgeries (see Figure S13, Supplementary material). This prophylaxis modality did not demonstrate a significant benefit, with moderate but significant heterogenicity (44%, $p > 0.10$), and an NNT equal to 10. Therefore, it can be stated that from literature analysis, no advantages emerged for the pre-surgical prophylaxis with amoxicillin in the case of osteotomy.

The meta-analysis of the data regarding pre-surgical prophylaxis with non-penicillin antibiotics in case of osteotomy included 2 studies for a total of 123 surgeries (see Figure S14, Supplementary material). The RR was significantly in favor of prophylaxis with both the fixed and random models, with an identical value (0.22). Furthermore, the heterogenicity of the studies was zero and the NNT was equal to 4. Therefore, it can be stated that from the analysis of the literature, the results homogeneously indicate a favorable effect in favor of pre-surgical administration of non-penicillin antibiotics in case of osteotomy.

Overall, in the case of osteotomy, the pre-surgical administration of antibiotics for the prophylaxis of surgical site infections following the extraction of the mandibular third molar has a significant efficacy.

However, this result is not homogeneous in the scientific literature because of the presence of studies that consider the use of amoxicillin, which also has not proved useful in the prevention of postoperative infections of the surgical site in case of osteotomy. Instead, data in literature unanimously indicate a significant and clinically important efficacy for pre-surgical prophylaxis with non-penicillin antibiotics in case of osteotomy.

The meta-analysis of the data regarding pre- and post-surgical prophylaxis with all types of antibiotics in case of osteotomy, included 7 studies for a total of 940 surgeries

(see Figure S15, Supplementary material). In this case, the RR significantly in favor of administering prophylaxis, was 0.56 both with the fixed and random models. Furthermore, the heterogenicity of the data was found to be zero and the NNT was equal to 28. Therefore, it can be stated that the literature homogeneously indicates a favorable effect in favor of pre- and post-surgical prophylactic antibiotics in case of osteotomy.

The pre- and post-surgical amoxicillin in the case of osteotomy was evaluated on the basis of 4 studies, for a total of 612 surgeries (see Figure S16, Supplementary material). This prophylaxis did not show a significant benefit, with zero heterogenicity. Therefore, it is possible to state that from the analysis of the literature no advantages emerged in the pre- and post-surgical prophylaxis with penicillin antibiotic in case of osteotomy.

The meta-analysis of the data regarding pre- and post-surgical prophylaxis with non-penicillin antibiotics in the case of osteotomy included 3 studies for a total of 328 surgeries (see Figure S17, Supplementary material). The RR was significantly in favor of prophylaxis with both the fixed and random models, with an identical value (0.47). Furthermore, the heterogenicity of the data was mild and not significant (10%, $p > 0.10$) and the NNT was equal to 13. Therefore, it is possible to state that the literature homogeneously indicates a favorable effect in favor of the pre- and post- surgical administration of non-penicillin antibiotics in case of osteotomy.

Overall, in case of osteotomy, the pre- and post- surgical administration of antibiotics for the prophylaxis of surgical wound infections following mandibular third molar extraction has a significant efficacy. However, this result is not homogeneous in the scientific literature due to studies that consider the use of amoxicillin, which also has not proved useful in the prevention of postoperative infections of the surgical site in case of osteotomy. Instead, the data in the literature unanimously indicate a significant and clinically important efficacy for pre- and post- surgical prophylaxis with non-penicillin antibiotics in case of osteotomy.

Post-surgical prophylaxis in the case of osteotomy has not shown any advantages either in the case of all antibiotics being considered (see Figure S18, Supplementary material) or in case only amoxicillin is considered (see Figure S19, Supplementary material). Furthermore, in the case of administration of non-penicillin antibiotics, it was not possible to perform a meta-analysis due to insufficient number of studies.

The analysis of data classified by odontotomy and the type of antibiotic did not yield significant results. Therefore, from the literature analysis, it is not possible to deduce that antibiotic prophylaxis, in any modality, is effective in case of only mandibular third molar odontotomy. Furthermore, it is not possible to say that penicillin antibiotics are more or less effective than non-penicillin ones (see Figures S20–S24, Supplementary material).

Some meta-analyses previously evaluated the effectiveness of antibiotic prophylaxis for the prevention of surgical wound infections following tooth extractions.

Ren and Malmstrom [1] published a meta-analysis in 2007 on mandibular third molars. They analyzed slightly fewer surgeries than we did (2396 vs. 2726 in the present study). That study, like the present one, found significant efficacy of pre- and post-surgical prophylaxis and a lack of efficacy of exclusively post-surgical prophylaxis. Unlike the present study, however, Ren and Malmstrom [1] reported an almost triple NNT (25 vs. 9 in the present study) for prophylaxis in general and a lack of significant efficacy of prophylaxis with non-penicillin antibiotics and exclusively pre- surgical one, even if a pre surgical single dose was reported nearly as effective as the multiday dosing strategy. These differences can be explained both by the inclusion of more recent studies in the present review, and by different inclusion criteria that led to the exclusion of studies that were included in the previous review.

The review by Gill and Coll. [42] concluded that there is little conclusive evidence to suggest the routine use of antibiotic prophylaxis for third molar extractive surgery in healthy young adults. However, this review did not perform a meta-analysis of the data and, although it was published in 2018, it only evaluated 4 studies compared to the 20 considered by Ren and Malmstrom [1] eleven years earlier.

Menon and Coll. [7] carried out a review and meta-analysis on the effectiveness of antibiotic prophylaxis without excluding the maxillary molars. On the other hand, clinical evidence suggests that the post- surgical course is completely different depending on whether the third molar is maxillary or mandibular, with a major onset and severity of complications in the mandibular arch. Furthermore, only studies on amoxicillin and amoxicillin with clavulanic acid were considered. The Authors reported a significant efficacy of prophylaxis for all modes of administration: pre-, post- surgical and mixed. They also reported a significant increase in complications related to the administration of post- surgical and mixed, but not pre- surgical, antibiotics.

Marcussen and Coll. [9] performed a meta-analysis on exclusively pre- surgical prophylaxis in the case of an operation involving osteotomy. The Authors reported a significant efficacy of prophylaxis both in case of amoxicillin and in case of other antibiotics. However, different inclusion criteria led to the exclusion of studies in the present review that were included by Marcussen and Coll [9].

A meta-analysis by Isiordia-Espinoza and Coll. [11] evaluated the efficacy of amoxicillin prophylaxis including fewer studies and without excluding surgery on maxillary molars. The authors reported an absence of significant efficacy of both pre- and post-surgical prophylaxis with amoxicillin.

The present meta-analysis illustrates the limitation of not having considered important patient-related factors such as sex, age, tobacco use, co-morbidities and concomitant drug therapies. This limitation is related to the fact that the included RCTs considered these factors as exclusion criteria or did not report the data distinctly. Generally, the presence of risk factors determines greater support to the need for antibiotic prophylaxis, but the judgment must be left to the surgeon.

Therefore, considering the foregoing, it seems possible to state that the data present in the literature homogeneously indicate a benefit in the administration of exclusively pre-surgical antibiotic prophylaxis with non-penicillin antibiotics; these data do not support the use of amoxicillin in some of the modalities considered and of non-penicillin antibiotics in post- surgical modalities. Pre- and post-surgical administration with non-penicillin antibiotics, although effective, seems clinically less impactful than pre-surgical administration.

5. Conclusions

This systematic review of the literature and meta-analysis evaluated the efficacy of antibiotic prophylaxis for the prevention of postoperative wound infection in case of mandibular third molar extraction. The inclusion and exclusion criteria were strongly selective. The results indicate that pre-surgical prophylaxis with antibiotics leads to a significant reduction of infections in the surgical site, except in case of odontotomy. Pre- and post-surgical and post-surgical prophylaxis alone demonstrated lower efficacy than pre-surgical prophylaxis alone. Furthermore, pre-surgical prophylaxis offers advantages in reducing the amount of antibiotics administered, lowering the risk of onset of antibiotic resistance and the appearance of side effects. Data from the literature suggest that antibiotic prophylaxis in case of extraction of mandibular third molar should be performed and should be done pre-surgically, except in case of odontotomy.

Supplementary Materials: The following data are available online at https://www.mdpi.com/article/10.3390/app11209449/s1, Table S1: Articles discarded after having read full articles, with reasons; Figure S1: Analysis of all the articles included in the study, comparing infections occurrence in antibiotic group, with no matter of the posology, and control one; Figure S2. Analysis of the articles considering prophylaxis therapy, comparing infections occurrence in antibiotic group and control one; Figure S3. Analysis of the articles considering prophylaxis therapy only with amoxicillin, comparing infections occurrence in infections occurrence in antibiotic group and control one; Figure S4. Analysis of the articles considering prophylaxis therapy with all type of antibiotic but amoxicillin, comparing infections occurrence in antibiotic group and control one; Figure S5. Analysis of the articles considering antibiotic therapy pre- and post- extraction, comparing infections occurrence in

antibiotic group and control one; Figure S6. Analysis of the articles considering antibiotic therapy pre- and post- extraction only with amoxicillin, comparing infections occurrence in antibiotic group and control one; Figure S7. Analysis of the articles considering antibiotic therapy pre- and post- extraction with all type of antibiotic but amoxicillin, comparing infections occurrence in antibiotic group and control one; Figure S8. Analysis of the articles considering antibiotic therapy post- extraction, comparing infections occurrence in antibiotic group and control one; Figure S9. Analysis of the articles considering antibiotic therapy post- extraction only with amoxicillin, comparing infections occurrence in antibiotic group and control one; Figure S10. Analysis of the articles considering antibiotic therapy post- extraction with all type of antibiotic but amoxicillin, comparing infections occurrence in antibiotic group and control one; Figure S11. Analysis of all the articles that considered osteotomy, comparing infections occurrence in antibiotic group, with no matter of the posology, and control one with osteotomy; Figure S12. Analysis of the articles that considered osteotomy and prophylaxis therapy, comparing infections occurrence in antibiotic group and control one, with osteotomy; Figure S13. Analysis of the articles that considered osteotomy and prophylaxis therapy only with amoxicillin, comparing infections occurrence in antibiotic group and control one with osteotomy; Figure S14. Analysis of the articles that considered osteotomy and prophylaxis therapy with all type of antibiotic but amoxicillin, comparing infections occurrence in antibiotic group and control one with osteotomy; Figure S15. Analysis of the articles that considered osteotomy and antibiotic therapy pre- and post- extraction, comparing infections occurrence in antibiotic group and control one with osteotomy; Figure S16. Analysis of the articles that considered osteotomy and antibiotic therapy pre- and post- extraction only with amoxicillin, comparing infections occurrence in antibiotic group and control one with osteotomy; Figure S17. Analysis of the articles that considered osteotomy and antibiotic therapy pre- and post- extraction with all type of antibiotic but amoxicillin, comparing infections occurrence in antibiotic group and control one with osteotomy; Figure S18. Analysis of the articles that considered osteotomy and antibiotic therapy post- extraction, comparing infections occurrence in antibiotic group and control one with osteotomy; Figure S19. Analysis of the articles that considered osteotomy and antibiotic therapy post- extraction only with amoxicillin, comparing infections occurrence in antibiotic group and control one with osteotomy; Figure S20. Analysis of all the articles that considered odontotomy, comparing infections occurrence in antibiotic group, with no matter of the posology, and control one with odontotomy; Figure S21. Analysis of the articles that considered odontotomy and prophylaxis therapy, comparing infections occurrence in antibiotic group and control one, with odontotomy; Figure S22. Analysis of the articles that considered odontotomy and prophylaxis therapy only with amoxicillin, comparing infections occurrence in antibiotic group and control one, with odontotomy; Figure S23. Analysis of the articles that considered odontotomy and antibiotic therapy pre- and post- extraction, comparing infections occurrence in antibiotic group and control one, with odontotomy; Figure S24. Analysis of the articles comparing groups treated with amoxicillin and groups treated with other antibiotics, with no matter of the posology.

Author Contributions: Conceptualization, S.M.L. and G.O.; methodology, C.T., J.L. and S.M.L.; data curation, G.O.; writing—original draft preparation, S.M.L., G.O., J.L., A.F., P.R., C.T. and R.R.y.B.; writing—review and editing, S.M.L. and G.O.; supervision, P.R. and R.R.y.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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