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Antibiotic prophylaxis in orthognathic surgery: an overview of systematic reviews

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Abstract

The purpose of this overview was to assess different antibiotic regimens used in orthognathic surgery and to establish an evidence-based protocol so that beneficial and adverse effects can be determined. A comprehensive literature search for systematic reviews and/or meta-analyses was conducted in MEDLINE (PubMed), EMBASE, and the Cochrane Library until March 2020. Grey literature was investigated in Google Scholar, and a manual search was done of references lists. Two meta-analyses and four systematic reviews met the inclusion criteria. The AMSTAR-2-tool was used to ascertain the potential risk of bias in the included studies, which presented moderate to high methodological quality. Lower infection rates were associated with long-term therapies of penicillin, cefazolin-cephalexin, and amoxicillin-clavulanic-acid, with rates varying from 0% - 3.13%. Higher rates were reported in placebo groups (52.6%) and short-term penicillin therapy (60%). Side effects were reported with cefazolin, clindamycin, and penicillin therapies, including nausea, pain, swelling, headache, vomiting, and skin rash. Evidence suggests that long-term antibiotics can reduce the risk of a surgical site infection (SSI) in orthognathic surgery, but there is uncertainty regarding the effects of one dose of antibiotics preoperatively versus short-term antibiotics. In the same way, intravenous penicillin, cefazolin, clindamycin, and amoxicillin-clavulanic acid kept the infection rates associated with bimaxillary procedures under 3.5%.

Keywords: orthognathic surgery; antibiotic therapy; antibiotic prophylaxis

Introduction

Orthognathic surgery (OS) is a consolidated surgical procedure to treat dentofacial deformities and their associated functional problems, such as physical pain, physical disability, cosmetic dissatisfaction, and difficulties with speaking, breathing, and chewing.[1,2] Patients can experience significant progress after the procedure since functional limitations decrease and quality of life improves.[1,2] However, despite the numerous advantages, complications including fever and swelling, nerve transection, sinusitis, deviated nasal septum, and surgical site infection (SSI) may occur. The most common complication is postoperative infection, with reports varying from 1.4% - 33.4%.[1,3,4]

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Postoperative infection is associated with discomfort, a prolonged period of hospitalisation, increased postoperative morbidity, and a higher cost of medical care.[5] Clinically, infection can be identified as purulent or positive serosanguineous drainage from the surgical site, pain or tenderness, localised swelling and redness of the wound margin and surrounding tissue, and an increase of body temperature to over 38.5 °C after 48 hours.[4] The risk factors that may be associated with a higher incidence of SSI after OS include longer surgeries, short-term antibiotic prophylaxis, extraction of a third molar during surgery, bad fractures, greater number of osteotomies, older age, smoking, poor oral hygiene, and a compromised immune system.[6–11] Although OS has been classified as clean contaminated surgery, Peterson[12] stated that it is possible to reduce infection rates to less than 1% if an excellent technique and antibiotic prophylaxis are used.

There are two main goals when using antibiotic prophylaxis: to provide an adequate drug level in the tissues before and during the procedure, and to provide the shortest possible entire administration period.[13] Many attempts have been made to determine the effects of antibiotic prophylaxis in patients undergoing OS and some studies have indicated that it may reduce the risk of SSI.[6,14–19] In accordance with this, a large number of systematic reviews have emerged and have combined these studies' findings to synthesise and extract the best evidence for treatment guidelines. Still, there is a lack of consensus concerning the use, timing, type, and dosage of antibiotic prophylaxis because of the diverse study outcomes.

Overviews of systematic reviews, which are studies with a high level of scientific evidence, aim to categorise and summarise secondary studies that respond to the same clinical question, or that complement each other in outcomes that may help clinicians in the decision-making process. The purpose of this overview was to assess the different antibiotic regimens used in OS and to establish an evidence-based protocol so that the beneficial and adverse effects of antibiotic prophylaxis for orthognathic surgery can be determined.

Material and methods

A comprehensive literature search for systematic reviews and/or meta-analyses was conducted using three strategies: the main search accessed MEDLINE (via PubMed), EMBASE, and the Cochrane Library databases; the second was a search of the grey literature through Google Scholar; and the third, a hand search of the references of the articles retrieved. The search was performed in accordance with the PICOS strategy (P: patients with dentofacial deformity requiring orthognathic surgery; I: antibiotic prophylaxis; C: differential antibiotic regimens; O: infection; S: systematic review OR meta-analysis). No limits were applied for language or year of publication, and Boolean operators (OR and AND) were used to combine subject headings related to dentofacial deformity, orthognathic surgery, antibacterial agents, and systematic review and/or meta-analysis. The MeSH terms used can be seen in the supplemental data (online only).

Study selection

All three searches were performed by one author (APSG), while the study selection was carried out independently by two authors (APSG and OLHJ). After analysis of the titles and abstracts, systematic reviews or meta-analyses on antibiotic prophylaxis in orthognathic surgery that were not narrative reviews of the literature, were selected for full-text reading.

Articles that did not meet these prerequisites were excluded. When one or two of the authors selected a study, it was read full-text. The eligibility of the selected articles was then assessed.

The kappa statistic (κ) was used to evaluate the level of agreement between APSG and OLHJ.

Study eligibility

After full-text reading, a standardised form was created and used to check the studies against the following criteria:

Studies that were not systematic reviews or meta-analyses with samples consisting exclusively of patients undergoing distraction osteogenesis, or patients with cleft lip and palate, or other syndromes;

Studies that reported summaries of the results of intervention and control groups after the administration of antibacterial drugs at the preoperative, perioperative, and postoperative periods;

Studies that included more than one primary study reporting infection rates in the absence and presence of prophylactic antibiotic therapy in orthognathic surgery procedures;

Original studies.

At this stage, in case of disagreement between the two investigators, the eligibility of the study was discussed with the other authors. Articles that did not meet the eligibility criteria were excluded from further analysis and the reason for exclusion reported.

Again, the kappa statistic (κ) was used to evaluate the level of agreement between APSG and OLHJ.

Data extraction

The same two independent authors extracted the demographic and methodological data, analysed the methodological quality, and assessed the prophylactic antibiotic regimens and associated infection rates from the systematic reviews included in this overview. In the event of disagreement, the article was discussed with the other authors, and if doubts persisted, the primary study to which the article in question referred was retrieved for analysis of crude results, or the corresponding author of the article was contacted via e-mail.

To standardise the results, three possible therapies were designated as follows: prophylactic antibiotic therapy in which patients received antibiotic intravenously at induction

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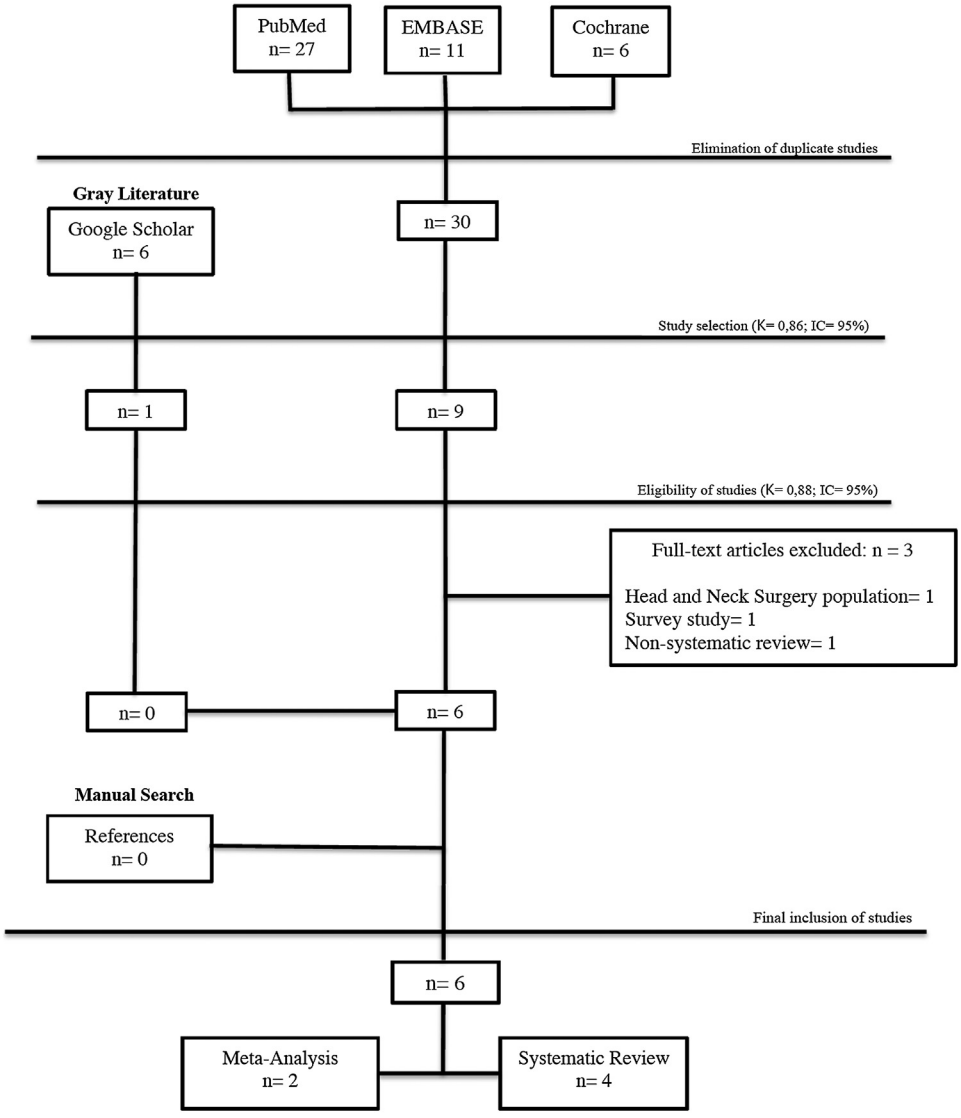

Fig. 1. Flowchart diagram.

or 30 minutes before surgery; short-term therapy in which patients received prophylactic treatment and antibiotic intravenously or orally for one or two days after surgery; and long-term therapy in which patients received prophylactic therapy and antibiotic intravenously or orally for three or more days after surgery.

Analysis of methodological quality

The criteria used by the systematic reviews or meta-analyses to assess the potential risk of bias of clinical trials were evaluated. The AMSTAR 2 tool[20] was used to ascertain the potential for risk in the secondary studies. The process of methodological quality analysis included 16 evaluation criteria for meta-analyses and 13 for systematic reviews. The criteria for evaluation of the methodological quality of the secondary studies were marked as follows: 'Yes' (Y) when included in the study methodology; 'No' (N) when not included; 'Partial yes' (PY) when partially included; and 'No meta-analysis conducted' (NMA) when the study was only a systematic review and the item was not applicable.

Results

With no restrictions on language or year of publication, and according to the protocols described, the main and the grey-literature searches were performed on 11 December 2020; the hand search of references of the included articles was performed on 12 December 2020 (Fig. 1).

Search strategy

Main search

The main search retrieved 27 studies from PubMed, 11 from EMBASE, and six from the Cochrane Library. After elimi-

nating duplicate records, 30 articles remained for screening of titles and abstracts.

Grey literature

A wide-ranging search of Google Scholar for articles published in non-indexed journals, designed to locate as many studies as possible, retrieved six items. Only one article remained for abstract screening.

Hand search

The hand search of references yielded no studies deemed worthy of inclusion.

Study selection

Screening of the titles and abstracts by the two independent authors resulted in an excellent level of agreement (κ = 0.86; 95% CI 0.68 to 0.99). Overall, nine articles from the main search were included. In case of disagreement between the authors, the article was nonetheless selected for full-text reading.

Study eligibility

The same authors independently evaluated the full text of all the articles selected in the preceding stage. After this step, the final sample included six articles, all of them retrieved from the main search. Agreement between the two authors during the eligibility assessment process was excellent (κ = 0.88; 95% CI 0.59 to 1.000).

Three papers were excluded because they did not meet the eligibility criteria. Of these, one included overall results collected from head and neck surgery patients,[21] one was a survey of oral and maxillofacial surgery residency programmes,[22] and one was not systematic review.[23]

Data extraction

Demographic data (Table 1)

Two meta-analyses[5,24] and four systematic reviews[25–28] were included in the final sample. The six studies collected data from14 randomised clinical trials (RCT), two retrospective cohort studies (RECO), two systematic reviews (SR), and three meta-analyses (MT). Of the studies' reporting samples,[5,25–27] a total of 2050 patients were evaluated, with ages ranging from 15 - 55 years. No information regarding the type of dentofacial deformity was reported. Surgical interventions varied from mandibular surgery only (bilateral sagittal split osteotomy (BSSO), intraoral vertical ramus osteotomy (IVRO), and genioplasty (GE))[16,19,29,30]; maxillary surgery only (Le Fort I osteotomy (LFO), and segmented maxillary osteotomy (SLFO))[15,17–19,31–33]; bimaxillary surgery and septoplasty[34]; or a combination of them.[6,15,17–19,31–35]

Only three studies[5,19,26] reported the criteria used to diagnose a SSI. This included purulent or positive-cultured serosanguineous drainage from the surgical site; pain or tenderness, localised swelling and redness of the wound margin and surrounding tissue; elevation of body temperature to

Table 1
Demographic data of the secondary studies.

First author, year, country of origin, and reference	Study	PICO	Sample	Type of primary study	Patients primary studies	Age (years)	Gender	Dentofacial deformity	Criteria for infection analysis	Follow up (weeks)
Tan 2011 China[5]	Meta-analysis	P = patients subjected to orthognatic surgery I = perioperative antibiotic prophylaxis in orthognathic surgery C = single day therapy; long-term therapy; placebo O = postoperative infection*	n = 5	5 RCT	n = 452	15-54	Male = 101 Female = 201	NR	1. Purulent or a positive-cultured serosanguineous drainage from surgical site 2. Pain or tenderness, localised swelling, and redness of the wound margin and surrounding tissue 3. Elevation of body temperature to 38.5 °C after 48 hours 4. Clinician diagnosis of infection	2-12

Table 1 (*Continued*)

First author, year, country of origin, and reference	Study	PICO	Sample	Type of primary study	Patients primary studies	Age (years)	Gender	Dentofacial deformity	Criteria for infection analysis	Follow up (weeks)
Danda 2011 India[24]	Meta-analysis	P = patients subjected to orthognatic surgery I = short-term (preoperative and perioperative) antibiotic therapy C = extended-term (preoperative, perioperative, and postoperative) antibiotic therapy O = postoperative wound infection*	n = 8	8 RCT	n = 532	23-29.9	Male = 203 Female = 299	NR	1. Purulent or a positive-cultured serosanguineous drainage from surgical site 2. Pain or tenderness, localised swelling, and redness of the wound margin and surrounding tissue 3. Elevation of body temperature to 38.5 °C after 48 hours 4. Clinician diagnosis of infection	2-12
Oomens 2014 Netherlands[25]	Systematic review	P = patients subjected to orthognatic surgery I = short-term (preoperative and perioperative) antibiotic therapy C = long-term therapy; placebo O = postoperative infection*	n = 11	11 RCT	n = 166 (3) NR (8)	NR	NR	NR	NR	NR
Brignardello-Petersen 2015 Chile[26]	Systematic review	P = patients subjected to orthognatic surgery I = any type of antibiotic, with any regimen or mode of administration (short-term or long-term; oral, endovenous, or intramuscular; preoperative or perioperative regimen) C = placebo, or another antibiotic, or another regimen of antibiotic O = postoperative surgical site infection*	n = 11	11 RCT	n = 788	15-55 (9) NR (2)	Male = 216 Female = 382 NR = 190		1. Purulent or positive-cultured serosanguineous drainage from surgical site 2. Pain or tenderness, localised swelling, and redness of the wound margin and surrounding tissue 3. Elevation of body temperature to 38.5 °C after 48 hours 4. Clinician diagnosis of infection	2-24

Table 1 (*Continued*)

First author, year, country of origin, and reference	Study	PICO	Sample	Type of primary study	Patients primary studies	Age (years)	Gender	Dentofacial deformity	Criteria for infection analysis	Follow up (weeks)
Naimi-Akbar 2018 India[27]	Systematic review	P = patients subjected to orthognatic surgery	n = 132	2 SR	n = 112 (2)	18-54 years (2)	Male = 80 (2)	NR	NR	6-12 (2)
		I = antibiotics on day of surgery (short-termed prophylaxis); antibiotics more than day of surgery (extended prophylaxis); head-to-head comparison of different antibiotic compounds or regiments		2 RCT	NR (12)	14 (NR)	Female = 32 (2)			NR (14)
		C = placebo; other non-antibiotic treatment; other/comparing antibiotic treatment (alternative compound); same compound, different dose/duration					NR (14)			
		O = infection, quality of life*								
Blatt 2019 Germany[28]	Systematic review	P = patients subjected to oral and maxillofacial surgery	n = 80**	2 SR	NR	NR	NR	NR	NR	NR
		I = oral and maxillofacial surgery	n = 10***	3 MT						
		C = antibiotics on day of surgery (short-termed prophylaxis); antibiotics more than day of surgery (extended prophylaxis); placebo; other/comparing antibiotic treatment (alternative compound); same compound, different dose/duration		3 RCT						
		O = postoperative surgical site infection*		2 RECO						

P: population, I: intervention; C: control; O: outcome; SR: systematic review; MT: meta-analysis; RCT: randomised controlled trial; RECO: retrospective cohort study; n: number of studies included; NR: not reported.

* Primary outcomes.

** Sample including other procedures than orthognathic surgery.

*** Sample including orthognathic patients only.

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38.5 °C after 48 hours; and clinician's diagnosis of infection. When reported, the follow-up period ranged from 2 - 24 weeks.[5,24,26,28]

Antibiotic therapies

There was a large variety of antibiotic treatment protocols and the period of administration ranged from preoperative, perioperative, and postoperative therapies, to a combination of them (Supplementary Table online only). Postoperative antibiotic therapies were further divided into those that were short-term (when extended until 2 days after surgery)[14–19,30–33,36] and long-term (when extended for 3 days or more).[14,15,17,18,29,31,33–35,37] Primary studies reported results using penicillin,[14,15,18,31,32,37] ampicillin,[19,35] cefpiramide,[36] amoxicillin,[17,18,30,36] and clindamycin,[16,32] and a combination of amoxicillin and clavulanic acid,[6,18] cefuroxime[6] and cefazolin,[9] cephalexin,[2,33] and levofloxacin[29] against placebo and/or each other. Lindeboom et al[16] reported adverse effects related to clindamycin, which included skin rashes or gastrointestinal disorders. Davis et al[32,33] reported adverse effects related to cefazolin,[33] which included nausea, pain, swelling, and headache; and effects associated with clindamycin, cefazolin and penicillin therapies,[32] which included nausea, vomiting, and skin rash.

The duration of surgery (when reported) varied from 0.7 - 8.45 hours, and only one study reported the hospital stay,[33] which was of 1 - 4 days.

Reported infection rates of primary studies

Reported postoperative infection rates ranged from 0%[18,29,31] - 60%,[15] and many different therapies were tested (Supplemenary Table online only). Lower infection rates were associated with long-term therapies of penicillin,[3] cefazolin and cephalexin,[29,34] and amoxicillin-clavulanic acid, with rates varying from 0% - 3.13%.[18] The short-term therapies of the above antibiotics also presented lower infection rates (3.03% for amoxicillin-clavulanic acid and 0% for penicillin and amoxicillin).[18] Other short-term therapies also presented lower values, including short-term ampicillin,[19] clindamycin,[16] and amoxicillin,[30] with infection rates of 2.6%, 2.8% and 3.33%, respectively (Fig. 2).

Higher rates were reported when antibiotic prophylaxis alone was tested against placebo,[6] with an infection rate for the placebo group of 52.6%. Bentley et al[15] reported the highest rate when comparing long-term versus short-term penicillin therapy, with infection rates of 6.67% and 60%, respectively.

Analysis of methodological quality

Methodological quality of clinical studies

Only one systematic review partially analysed the methodological quality of the primary studies[19] using a scale that had been customised by the authors themselves. The other five studies used tools developed specifically by expert groups to evaluate the methodological quality of primary studies: three used those recommended by the Cochrane Library,[5,26,28] one used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines,[27] and one the Delphi list and Jadad scale.[25]

The potential risk of bias in clinical trials was generally considered to be moderate to high.[14,18,29,30,32,34,36,37] In most primary studies the sample randomisation process was unclear, a condition that increases the potential risk of bias. Only one study[36] was rated as having a low risk of bias in all analyses. It was commonly found that the same study was classified as having high and moderate, moderate and low, and even a high, moderate, and low risks of bias[6,15,17,19] among the different scales used by the secondary studies (Table 2).

Methodological quality of systematic reviews

None of the secondary studies reported all the criteria evaluated by the AMSTAR 2 tool. Among the systematic reviews, the greatest methodological rigour was found in a review by Brignardello-Petersen et al,[26] who evaluated 12 of 13 possible items in the methodology section. Among meta-analyses, Tan and Zwahlen[5] reported 13 of 16 possible criteria. Overall, more items were present than were missing.

Individual analysis of the items that were used to verify potential risk of bias in systematic reviews revealed that only one article[25] partially reported conflicts of interest in the primary studies. On the other hand, all the studies reported the inclusion and exclusion criteria of the primary clinical trials. Only one meta-analysis had not established a written protocol prior to execution of the review.[24] Five studies[5,25–28] included some type of analysis of agreement between independent reviewers at the time of study selection/eligibility, or data extraction.

Discussion

This overview of systematic reviews was designed mainly to synthesise the information found in secondary studies on antibiotic prophylaxis in OS. The results of these papers were analysed for quality and synthesised to more easily understand the role of antibiotic prophylaxis in preventing postoperative infection in OS procedures.

The methodological rigour that is required to conduct an overview of systematic reviews must remain at the highest level if the quality of the scientific evidence generated is to be reliable. Taking this into account, the authors carried out an objective selection process so that methodological rigour could be maintained throughout the overview. The level of agreement between the authors during both the selection process (k = 0.86) and study eligibility assessment (k = 0.88) was considered excellent, demonstrating homogeneity in the generation of scientific evidence.

Despite the high level of methodological rigour, it is still possible to incorporate bias during data extraction. In fact, a great challenge of this study was to collect the data accurately,

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Table 2
Quality analysis of included studies with AMSTAR-2[20] (measurement tool to assess systematic reviews).

Study	Tan et al, 2011[5]	Danda and Ravi, 2011[24]	Oomens et al, 2014[25]	Brignardello-Petersen et al, 2015[26]	Naimi-Akbar, 2018 et al, 2018[27]	Blatt and Al-Nawas, 2019[28]
Did the research questions and inclusion criteria for the review include the components of PICO?	PY	Y	Y	Y	Y	Y
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y	N	Y	Y	Y	Y
Did the review authors explain their selection of the study designs for inclusion in the review?	Y	Y	Y	Y	Y	Y
Did the review authors use a comprehensive literature search strategy?	Y	PY	Y	Y	Y	PY
Did the review authors perform study selection in duplicate?	Y	N	Y	Y	Y	N
Did the review authors perform data extraction in duplicate?	Y	N	PY	Y	N	N
Did the review authors provide a list of excluded studies and justify the exclusions?	Y	PY	N	Y	Y	N
Did the review authors describe the included studies in adequate detail?	Y	Y	PY	Y	Y	PY
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y	PY	Y	Y	Y	Y
Did the review authors report on the sources of funding for the studies included in the review?	N	N	PY	N	N	N
If meta- analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Y	Y	NM	NM	NM	NM
If meta- analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y	Y	NM	NM	NM	NM
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y	Y	Y	Y	Y	Y
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y	N	Y	Y	Y	PY
If meta- analysis was performed, did the review authors carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review?						
If meta- analysis was performed, did the review authors carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review?	Y	Y	NM	NM	NM	NM
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	N	N	Y	Y	N	Y
Risk of bias	Y(13) PY(1) N(2)	Y(7) PY(3) N(6)	Y(9) PY(3) N(1)	Y(12) N(1)	Y(10) N(3)	Y(6) PY(3) N(4)

Y: yes; N: no; PY: partial yes; NM: no meta-analysis.

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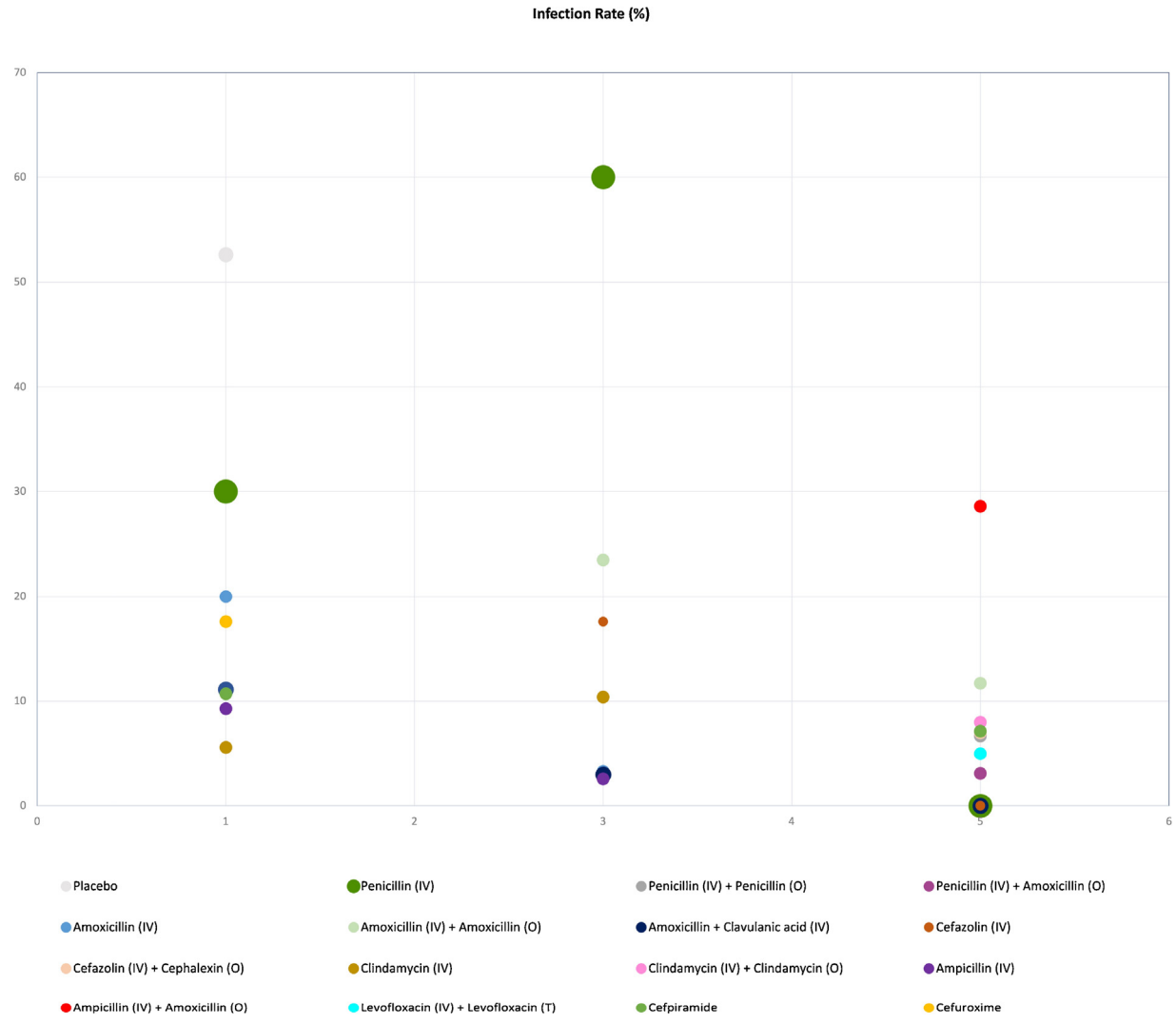

Fig. 2. Reported infection rates (%) of different antibiotic therapies: preoperative or single-day therapy (1 day); short-term therapy (3 days); and long-term therapy (5 days).

since data in four of the six secondary studies were reported incorrectly or were missing.[5,25,26,28] Careful revision of each primary study was necessary to adjust incorrect data. The secondary studies assessed 14 clinical trials (considered mostly to have a high, moderate or unclear risk of bias) and two retrospective cohort studies. Although only one study used a customised quality assessment scale,[24] methodological analysis of the primary studies did not show similar patterns, with only one study being considered to have a low risk of bias on all analyses.[36] The main lack of methodological criteria was associated with an unclear randomisation process and blinding of assessors, and made the quality assessment doubtful (Table 2).

Although the primary studies were classified generally as having a moderate to unclear risk of bias, the systematic reviews that included them were deemed to have a moderate to high methodological quality, as more AMSTAR 2 items[20] ('Yes') were present than absent ('No') (Table 2). Taking this into account, we believe that this overview has synthesised the current scientific evidence on antibiotic prophylaxis for OS, and that postoperative infection rates may indicate a clear path and help clinicians to make better decisions in clinical practice (Fig. 3).

OS is a clean contaminated procedure that is expected to have higher infection rates than non-contaminated surgery.[25] The development of wound infection is a complex interaction between intraoperative bacterial inoculation and various factors of the host's local and systemic resistance to infection.[5] Although operating time, patient's age, and hospitalisation after surgery were considered important factors affecting wound infection, there is a lack of reported data among clinical trials to support them.[1,5,26] Still, some agreement can be found concerning recommendations for the use of prophylactic antibiotic regimens for medically compromised patients or surgery requiring bone grafts.[38,39]

According to Chow et al,[1] the pathogens most commonly associated with SSI after OS are anaerobic bacteria, which have been observed in 50% of pus samples of SSI after OS,

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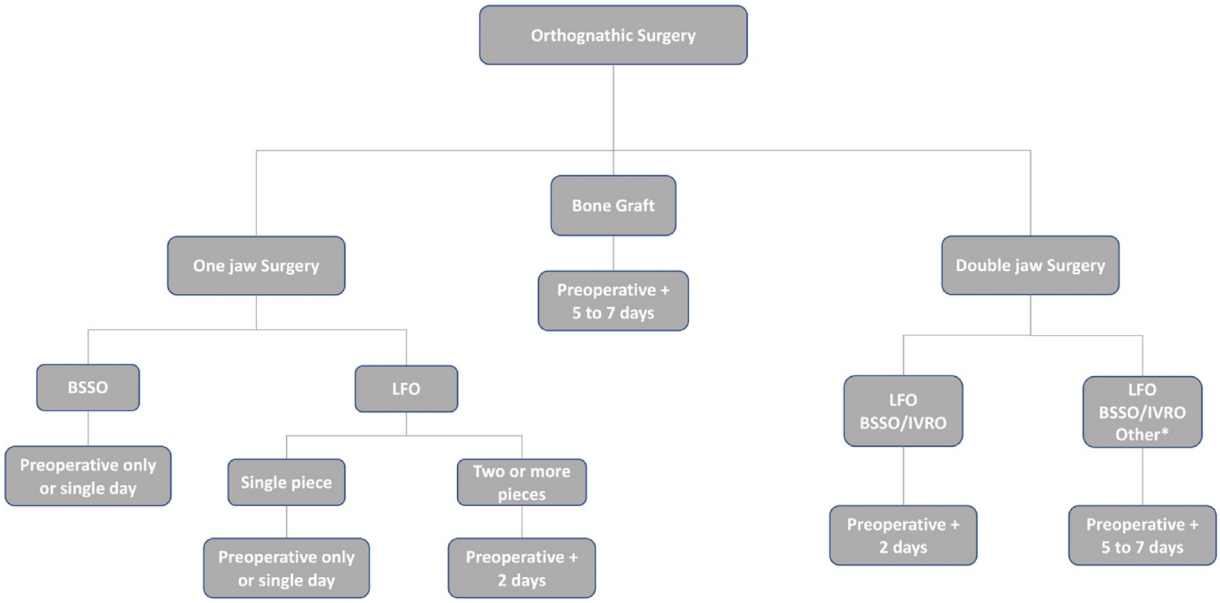

Fig. 3. Decision-making workflow for antibiotic prophylaxis in orthognathic surgery.
*Other: Genioplasty, rhinoplasty, bone augmentation; bilateral sagittal split osteotomy (BSSO); Le Fort I osteotomy (LFO); intraoral vertical ramus osteotomy (IVRO).

and streptococci, which have been observed in 43% of cases. As for the specific substance, cefazolin and aminopenicillins were used the most in the different regimens.[28] Penicillin is considered effective against most oral pathogens and has been recommended to prevent infection during intraoral procedures.[3,8,12,15,18,22,31] In their meta-analysis, Danda and Ravi[24] included six RCTs that used penicillin-group antibiotics, and recommended their use in OS. In contrast, Blatt and Al-Nawas[28] evaluated studies with a high risk of bias and concluded that cefazolin was more effective than penicillin and clindamycin when antibiotic therapy was recommended,[32,33] but the relatively high number to treat (up to 10) led to uncertainty with respect to the preferred compound and optimal range of prophylaxis.[27,33]

Although debate still exists regarding the best route of administration and type of antibiotic, there is consensus in the literature that a preoperative dose effectively reduces postoperative infections after OS.[5–28] The RCT by Zijderveld et al[6] was the only one to compare antibiotic prophylaxis with placebo. They demonstrated the importance of prophylactic antibiotics by detecting a significantly increased risk of infective complications (52.6%) after bimaxillary orthognathic surgery in the placebo group. Based on these results, Oomens et al[25] concluded that one in every 2.61 patients who has received antibiotic prophylaxis will benefit from the treatment compared with controls. The initial dose should be administered parenterally until 30 minutes before the operation, otherwise it is considered to be associated with an increased wound infection rate.[5,12,40,41]

Whether or not the antibiotic therapy should be continued has been widely discussed. While Lindeboom et al[16] reported an infection rate of 5.6% when a single intravenous dose of clindamycin 600 mg was used before mandibular surgery (BSSO), Wahab et al[30] reported an infection rate of 20% with amoxicillin 1 g for the same procedure. For bimaxillary surgery, ampicillin seemed to be the most effective, with an infection rate of 9.3%,[24] followed by cefpiramide 1 g (10.71%)[36] and amoxicillin-clavulanic acid 2.2 g (11.11%).[6] Despite infection rates mostly being higher than those reported with short and long-term therapies,[30,37] Oomens et al[25] found no evidence of the effectiveness of continuous postoperative antibiotics[16,35] and no difference in infection rates in patients who were given a single dose or a single-day regimen. Brignardello-Petersen et al[26] statistically analysed the results of two RCTs[16,19] and reported that whilst participants who received short-term antibiotic prophylaxis were less likely to develop an SSI than those who received a single, preoperative dose, no evidence of statistical heterogeneity was found.[26] A single preoperative dose or a single-day treatment seems to effectively control postoperative SSI in one-jaw surgery when BSSO or one-piece Le Fort I osteotomy is performed.[16,19,30,32]

The most effective short-term therapies seem to be ampicillin 1 g, with an infection rate of 2.6%[19] followed by amoxicillin-clavulanic acid 1.2 g, with an infection rate of 3.03%,[18] both intravenously. Generally, primary studies reported a wide range of infection rates for short-term therapies, which varied from 0%[18] - 60%[15] for penicillin, 2.8%[16] - 10.4%[32] for clindamycin, 6.4%[32] - 17.6%[33] for cefazolin, and 3.03%[18] - 25.5%[17] for amoxicillin. The wide variety of rates between studies can be explained (in most cases) by differences in the extent of the surgical procedure, duration of surgery, and antibiotic doses (Supplementary Table online only). Short-term therapies may be reasonably applied

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to single-jaw OS when segmented Le Fort I is performed, and to double-jaw OS when one-piece Le Fort I osteotomy and BSSO/IVRO are performed, and to operations that last no more than five hours.[18,19,32]

The lowest postoperative infection rates were associated with long-term intravenous and oral amoxicillin-clavulanic acid, intravenous penicillin, and intravenous cefazolin therapies.[18,31] Three studies[5,24,26] presented similar findings and tended to agree that patients who received antibiotic prophylaxis for longer were less likely to develop postoperative infections. Although Tan and Zwahlen,[5] Oomens et al,[25] and Blatt and Al-Nawas[28] found no evidence of the effectiveness of prolonged antibiotics, Danda and Ravi[24] showed in their meta-analysis that long-term prophylaxis of between one and seven days presented lower postoperative infection rates. They also concluded that patients receiving longer-term antibiotics were 3.2 times less likely to develop postoperative wound infections than patients on short-term antibiotics. Brignardello-Petersen et al[26] reported a reduction in the absolute risk of developing a SSI from 168 SSIs/1000 surgeries with short-term antibiotics to 71 SSIs/1000 surgeries with long-term antibiotics. This therapy may be better indicated for double-jaw OS when it is associated with other procedures, such as genioplasty, rhinoplasty, and bone augmentation, and when surgery lasts for more than five hours.[15,18,31–34] Still, it must be considered that the only outcome for which beneficial evidence was found was the incidence of SSI; other outcomes of importance were poorly reported, such as costs, disturbance of microbial flora, and side effects.

Broadly, side effects were poorly investigated and described. The studies retrieved information based on only two RCTs.[32,33] These in turn reported adverse effects related to cefazolin therapy,[3] which included nausea, pain, swelling, and headache; and those associated with clindamycin, cefazolin and penicillin therapies,[32] which included nausea, vomiting, and skin rash. It could be considered a severe flaw, as it is widely known that besides the side effects, extended antibiotic therapy may predispose to the development of resistant bacterial strains, changes in physiological host flora, secondary infection, and increased health care costs.[3,6,8,12,31,40,42,43]

Overall, the secondary studies evaluated a broad sample of participants who were treated in different settings and with different regimens of antibiotic prophylaxis. In addition to this, results were similar among trials, and this favours the applicability of the evidence to many populations and settings. Even though more well-reported, low-risk of bias research, (including power calculations) is needed, evidence suggests that long-term antibiotics can reduce the risk of SSI in OS, although there is uncertainty regarding the effect of receiving one dose preoperatively versus short-term use. In the same way, intravenous penicillin, cefazolin, clindamycin and amoxicillin-clavulanic acid kept infection rates associated with bimaxillary procedures under 3.5%. Nonetheless, it must be remembered that the only adverse effects that were reported were associated with their use. These results still indicate that clinicians should carefully weigh the advantages against the disadvantages of prescribing postoperative antibiotics for each individual patient, and it remains of the utmost importance to ration their use and keep the levels of antibiotic resistance to a minimum.

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Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Not applicable.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjoms.2021.05.010.

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