REVIEW

A systematic review of latest evidence for antibiotic prophylaxis and therapy in oral and maxillofacial surgery

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Abstract

Purpose Especially in oral and maxillofacial surgery, where procedures involving the aero-digestive tract considered clean contaminated, surgical site infections (SSI) represent a severe health care burden. To improve implementation and methodological standard, an upgrade of the existing S1 guideline to a consensus-guided S3 guideline was initiated by the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF, register number 067/009) and 25 collaborating medical societies.

Methods A systematic literature search based on the Scottish Intercollegiate GL Network (SIGN)-search string for the guideline "Antibiotic prophylaxis in surgery" from 2014 was performed and equivalent exclusion/inclusion criteria were applied. An additional hand search provided latest evidence.

Results In total, 80 clinical trials, retrospective studies, reviews, and meta-analysis were analyzed. For orthognathic surgery, prolonged antibiotic regimen may reduce risk for SSI but there is lack of evidence for the effects of short- vs. long-term therapy. For maxillofacial traumatology, antibiotic prophylaxis might reduce SSI but prolonged postoperative dosing shows no benefit. For clean-contaminated oncological interventions, anti-infectious therapy for 24 h only can reduce SSI; patients may not benefit from prolonged regimen. In contrast, for dentoalveolar procedures such as implantology or third molar removal, literature reveals ambivalent results.

Conclusion In summary, consensus process of the planned S3 guideline is much in need to transfer the indecisive results for antibiotic prophylaxis in dentoalveolar surgery in clinical praxis and encourage adherence to guidelines.

Keywords Antibiotic prophylaxis · Nosocomial infection · Anti-infectious therapy · Maxillofacial surgery

Introduction

Perioperative antibiotics are generally used in surgery to prevent surgical site infections (SSI). By definition, a SSI is an infection that develops within 30 days after an operation or within 1 year of an implant being placed, where the infection appears to be related to the surgery [1]. Prevalence of SSI depends very much on variety of the procedure. The American Society of Health-System Pharmacists (ASHP) categorizes surgery in four different classes that, in the context of this study, are subsequently listed with typical examples of respective procedures in oral and maxillofacial surgery: clean (e.g., atraumatic procedures or where neither the gastrointestinal, genitourinary, nor respiratory tracts is violated such as cervical lymph node excisions), clean-contaminated (e.g., procedures that violate the gastrointestinal or respiratory tract such as parotidectomy, submandibular gland excision, third molar removal), contaminated (e.g., surgery in acute inflammation situation such as open mandible fracture repair with osteosynthesis) and dirty (e.g., procedures involving pus or compound/open injuries such as dentogenic abscess incision) [2].

In contrast to therapeutically used antibiotics, the perioperative treatment aims to reduce contamination of the (physiological) bacterial flora in the specific surgical area. The basic purpose of antibiotic prophylaxis is, therefore, to provide an adequate drug level in the tissues before, during, and for the shortest possible time after the procedure [3]. Prophylactic antibiotic treatment is defined as the use of antibiotics before, during, or after a diagnostic, therapeutic, or surgical procedure to prevent infectious complications. Here,

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the Scottish Intercollegiate GL Network (SIGN) guideline "Antibiotic prophylaxis in surgery" defines two regimens; the short-term prophylaxis administered any time before or after surgery for up to 24 h after the surgical intervention and long-term antibiotic prophylaxis that is continued for longer than 24 h. In contrast, therapeutic antibiotic treatment is used to reduce the growth or reproduction of bacteria, including eradication therapy. Antimicrobial therapy is then prescribed to clear infection by an organism or to clear an organism that is colonizing a patient but is not causing infection [4].

In Europe and the US, SSI represents second-most common hospital-acquired infections and are greatly responsible for prolonged stay and lethality [5]. Especially in head and neck surgery and maxillofacial procedures, where the aerodigestive tract is involved and operations are frequently considered clean contaminated, SSI represents a severe health burden with an incidence of up to 10–15% [3].

However, unreasonable and excessive use of antibiotics is not only uneconomical but also involves the risk for developing multiple drug resistance in bacteria which is claimed to be a major cause of the failure of therapy in many human infections [6]. Therefore, appropriate use of antibiotics is seen as a national health priority to prevent the morbidity of infections and the development of resistant organisms [7]. It has been estimated that approximately half of SSIs are preventable by application of evidence-based strategies [8]. To minimize SSI and appearance of multidrug resistance mechanisms in head and neck surgery, the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF, register number 067/009) and 25 collaborated medical societies initiate an upgrade of the existing S1-guideline "Antibiotics in surgery" to a consensus-guided S3 guideline. The systemic literature search is based on the search string of the SIGN guideline "Antibiotic prophylaxis in surgery" from 2014 [4]. Herein, the latest evidence for antibiotic therapy in oral and maxillofacial and dentoalveolar surgery is summarized.

Materials and methods

A Medline literature search was performed via Pubmed and Ovid following the search narrative of the SIGN guideline "Antibiotic prophylaxis in surgery" from 2014 [4]. This way, evidence base of the respective surgical specialties for the planned guideline was produced in accordance with high standards of the SIGN methodology. The search was carried out between 06/30/2015 and 07/01/2016. Latest update was 06/30/2016. The search was initially filtered for the period between 2010 and 2015. To update the review with the latest evidence for head and neck surgery between 2015 and

2018, a hand search was made on August 2018. Search terms were "perioperative antibiotic prophylaxis" in addition to "maxillofacial surgery"," head and neck", "dental surgery", "cranio-maxillofacial surgery", "maxillofacial surgery", "orthognathic surgery", "midfacial fractures", "cleft palate surgery", "third molar removal", "mronj", "dentogenic abscess", and "dental implant". In accordance with the SIGN guideline, the following topics were excluded from further analysis:

- Prevention of endocarditis after surgery or instrumentation.
- Use of antiseptics for the prevention of wound infection after elective surgery.
- Treatment of anticipated infection in patients undergoing emergency surgery for contaminated or dirty operations.
- Administration of oral antibiotics for bowel preparation or to achieve selective decontamination of the gut.
- Most topical antibiotic administration, for example, in wounds or for perineal lavage.
- Use of antibiotics for prophylaxis in patients with prosthetic implants undergoing dental surgery or other surgery that may cause bacteraemia.
- Transplant surgery.

As inclusion criteria, we reviewed all randomized and not randomized clinical trials, in vivo and ex vivo prospective as well as retrospective studies investigating perioperative antibiotic prophylaxis in surgery that were in English or German language. After full-text screening, the major indicator study type (clinical trial, retrospective, etc.), investigated parameter (in all cases SSI), intervention (performed oral and maxillofacial surgery procedure), comparison (antibiotic regimen, timing and dosing if indicated) and outcome were extracted (Table 2). Furthermore, the risk of bias for every included study was analyzed by the criteria recommended by the Cochrane Library [9]. A study that met all the criteria was classified as having a low risk of bias. When two or more criteria were not met, the study was considered to have a high risk of bias (Table 1).

Results

The search showed 5784 hits for all surgical procedures between 2010 and 2015. After title/abstract screening and exclusion of 89 duplicates, 316 studies were included for full-text analysis without filter for the respective discipline-specific surgical interventions. Concerning perioperative prophylaxis in oral and maxillofacial surgery, 69 studies could be extracted. Here, a total of 32 studies referred to neurosurgical, ear, nose and throat or ophthalmological procedures. The remaining 37 hits (14 meta-analysis/reviews,

Table 1 Risk of bias analyzed for the obtained studies following recommendations of the Cochrane library in alphabetically order

Refs.	n	Allocation	Assessor blinding	Patient blinding	Withdrawals	Risk of bias
Adalarasan et al. 2010 [30]	67	Unclear	None	None	None	High
Arduino et al. 2015 [77]	360	Adequate	Yes	Yes	Yes	Low
Arteagoitia et al. 2015 [50]	118	Adequate	Yes	Yes	Yes, reasons given	Low
Arteagoitia et al. 2015 [50]	10 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Ata-Ali et al. 2014 [68]	4 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Aznar et al. 2015 [32]	546	Adequate	Yes	Yes	Yes, reasons given	Low
Bartella et al. 2017 [43]	75	None	None	None	Not stated	High
Bartella et al. 2018 [82]	901	Not adequate	None	None	Yes	Moderate/high
Bezerra et al. 2011 [51]	45	Adequate	Yes	Yes	Yes, reasons given	Low
Brignardello-Petersen et al. 2015 [14]	11 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Cachovan et al. 2011 [80]	71	Adequate	Yes	Yes	Yes, reasons given	Low
Campos et al. 2015 [25]	74	Not stated	None	Not stated	Not stated	Moderate
Cannon et al. 2017 [42]	19 studies	Not stated	Not stated	Not stated	Not stated	Low/moderate
Carcuac et al. 2016 [78]	100	Yes	Yes	Yes	Yes	Low
Cho et al. 2017 [61]	221 studies	Not stated	Not stated	Not stated	Not stated	Moderate
Chrcanovic et al. 2014 [70]	14 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Danda et al. 2010 [13]	150	Unclear	Yes	Yes	None	Moderate
Danda et al. 2011 [12]	8 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Davis et al. 2016 [15]	2268	None	None	None	Yes	High
Davis et al. 2017 [17]	179	Adequate	Yes	Yes	Yes	Low
El-Kholey 2014 [75]	80	Adequate	Yes	Yes	None	Low
Esposito et al. 2013 [69]	6 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Gaal et al. 2016 [24]	510	None	None	None	None	High
Gomez-Arambula et al. 2015 [81]	21	Not stated	None	None	Yes	Moderate
Habib et al. 2018 [26]	13 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Hallstrom et al. 2017 [79]	39	Adequate	Yes	No	Yes	Low/moderate
Hammond et al. 2017 [27]	708	None	None	None	None	High
Hindawi et al. 2011 [88]	197	None	None	None	None	High
Hoefert et al. 2011 [36]	46	None	None	None	None	High

Table 1 (continued)

Refs.	n	Allocation	Assessor blinding	Patient blinding	Withdrawals	Risk of bias
Huang et al. 2015 [31]	160	None	None	None	None	High
Iglesias-Martin et al. 2014 [49]	546	Adequate	None	None	None	Moderate/high
Isiordia-Espinoza et al. 2015 [60]	15 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Knepil et al. 2010 [86]	134	None	None	None	None	High
Koshkareva et al. 2014 [37]	Not stated	Not stated	Not stated	Not stated	Not stated	Low
Krasny et al. 2016 [74]	1915	None	None	None	None	High
Kruse et al. 2010 [38]	Not stated	Not stated	Not stated	Not stated	Not stated	Low
Lang et al. 2017 [63]	2954	None	None	None	Yes	Moderate/high
Langermann et al. 2017 [89]	8836	None	None	None	None	High
Lauder et al. 2010 [22]	223	None	None	None	None	High
Lee et al. 2014 [48]	890	None	None	None	None	High
Lopez-Cedrun et al. 2011 [62]	123	Adequate	Yes	Yes	None	Low
Lund et al. 2015 [71]	17 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Low
Man et al. 2011 [40]	244	None	None	None	None	High
Marcussen et al. 2016 [66]	10 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Low
Marghalani 2014 [59]	18 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Martin-Ares et al. 2017 [54]	293	Not stated	Not stated	Yes	Yes, reasons given	Low/moderate
Mercuri 2012 [1]	2 studies	Not stated	Not stated	Not stated	Not stated	High
Milani et al. 2015 [56]	83	Adequate	Yes	Yes	Yes	Low
Morris et al. 2014 [19]	6 studies	Not stated	Not stated	Not stated	Not stated	Low
Mottini et al. 2014 [21]	339	None	None	None	None	High
Murphy et al. 2017 [45]	102	None	None	None	None	High
Naimi-Akbar et al. 2017 [18]	19 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Low
Nolan et al. 2014 [73]	55	Unclear	Yes	Yes	Yes	Low
Oomens et al. 2014 [11]	11 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Park et al. 2018 [76]	15 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Low
Pasupathy et al. 2011 [53]	89	Adequate	Yes	Yes	Yes	Low
Perepa et al. 2018 [28]	144	Not stated	Yes	Not stated	Unclear	Low/moderate
Posnick et al. 2016 [16]	262	None	None	None	None	High

Table 1 (continued)

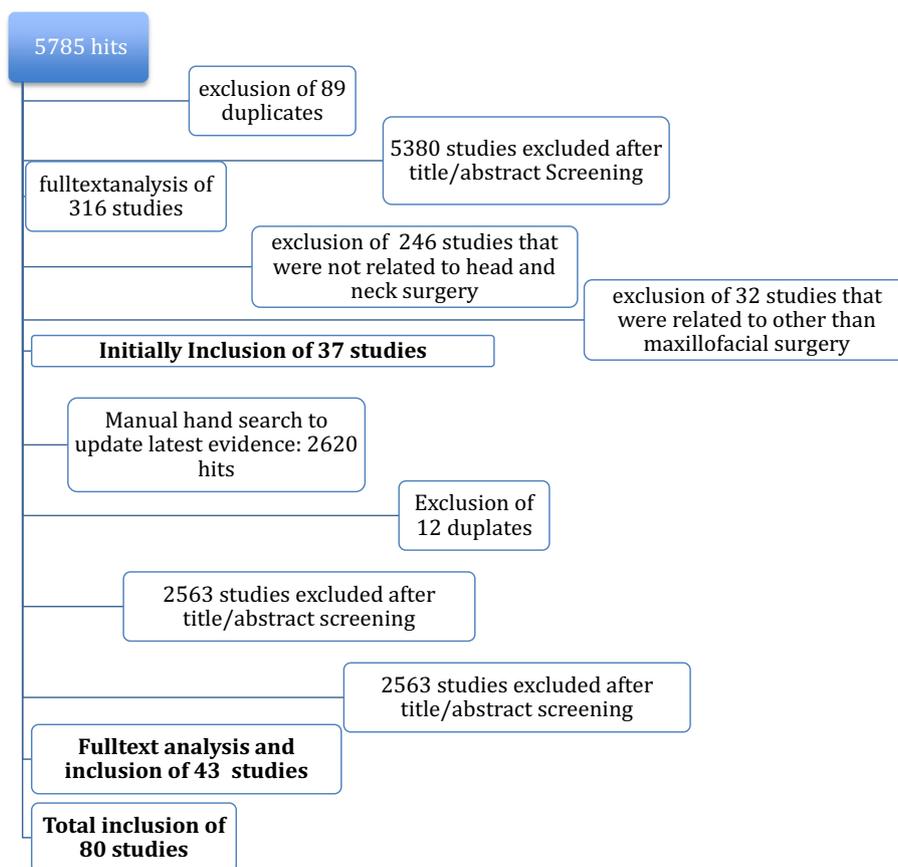| Refs.	n	Allocation	Assessor blinding	Patient blinding	Withdrawals	Risk of bias
Prajapati et al. 2016 [57]	40	None	None	None	None	High
Ramos et al. 2016 [65]	22 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Low
Reiland et al. 2017 [58]	1895	None	None	None	None	High
Rosengren et al. 2018 [47]	154	Adequate	Yes	Yes	Yes	Low
Russell et al. 2012 [39]	5 studies	Not stated	Not stated	Not stated	Not stated	Low
Sayd 2018 et al. [71]	108	None	None	None	None	High
Schaefer et al. 2013 [29]	79	None	None	None	None	High
Schaller et al. 2013 [20]	59	Adequate	Yes	Yes	Yes	Low
Sharaf et al. 2011 [72]	8 studies	Not stated	Not stated	Not stated	Not stated	Low
Shkedy 2016 et al. [46]	593	None	None	None	None	High
Sidana et al. 2017 [67]	171	Adequate	Yes	Yes	Yes	Low
Soong et al. 2014 [23]	98	Adequate	Yes	Yes	Yes	Low
Tan et al. 2011 [10]	5 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Very low
Veve et al. 2017 [44]	34 studies	Not stated	Not stated	Not stated	Not stated	Low/moderate
Vila et al. 2017 [41]	4 studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Investigated in respective studies	Low
Waasdorp et al. 2010 [84]	Not stated	Not stated	Not stated	Not stated	Not stated	Low
Wahab et al. 2013 [3]	60	Unclear	Unclear	Unclear	Unclear	High
Xue et al. 2015 [52]	192	Adequate	Yes	Yes	Yes	Low
Zirk et al. 2017 [35]	143	None	None	None	None	High

13 randomized clinical trials (RCT) and 10 retrospective clinical studies) analyzed prophylaxis in procedures of maxillofacial surgery in the timeframe of 2010–2015. In August 2018, an additional hand search was made to update latest evidence for maxillofacial surgery. Here, filtered for the years between 2015 and 2018, a total of 2620 hits could be found and after title and abstract screening and exclusion of 12 duplicates, a total of 43 objects met the inclusion criteria and were implemented in the full-text analysis. Altogether, a total of 80 studies were included in this review (Fig. 1). The recommendations of these studies concerning the perioperative antibiotic prophylaxis and therapy are summarized, namely the major indicator study type, investigated parameter, intervention, comparison and outcome (Table 2).

For orthognathic surgery, 10 studies could be obtained that show the benefit of perioperative prophylaxis with low to high risk of bias. In majority, there was no statistically significant difference between rates of infection in single dose prophylaxis vs. long-term dosing [10–13]. A study with high risk of bias demonstrated a short postoperative course of antibiotics as more effective than a single preoperative dose in cases of bilateral sagittal split osteotomy [3]. In addition, a Cochrane review concluded that there is moderate-quality evidence for SSI risk reduction with long-term antibiotic prophylaxis [14]. As suitable substances, cefazolin appears to be more effective than penicillin and clindamycin but with high risk of bias [15, 16]. Furthermore, the number needed to treat was relative high which leads to uncertainty with respect to the preferred antibiotic compound and the optimal range of the prophylaxis [17, 18].

16 studies evaluated antibiotic prophylaxis in maxillofacial traumatology but differed in quality of study design with low to high risk of bias. A 1-day postoperative course of antibiotic is effective in preventing infective complications. No additional benefit of postoperative antibiotic prophylaxis could be found [19–28]. As a suitable antibiotic compound,

Fig. 1 The selection process of evidence within the systematically and manually literature search is illustrated

5785 hits

exclusion of 89 duplicates

5380 studies excluded after title/abstract Screening

fulltextanalysis of 316 studies

exclusion of 246 studies that were not related to head and neck surgery

exclusion of 32 studies that were related to other than maxillofacial surgery

Initially Inclusion of 37 studies

Manual hand search to update latest evidence: 2620 hits

Exclusion of 12 duplates

2563 studies excluded after title/abstract screening

2563 studies excluded after title/abstract screening

Fulltext analysis and inclusion of 43 studies

Total inclusion of 80 studies

ampicillin/sulbactam seems to be superior to clindamycin [29]. Furthermore, a retrospective study with high risk of bias found no statistical significant difference between a regime of penicillin and cefotaxime [30]. Another retrospective study even questions the use of prophylactic antibiotics in orbitozygomatical fractures [31]. For temporomandibular joint replacement, perioperative prophylaxis is efficient in reducing SSI [1]. In cleft palate surgery, three studies could be found but no benefit of postoperative antibiotics was seen to prevent SSI [32–34]. Two studies, retrospectively only with high risk of bias, found long-term antibiotic treatment useful to prevent recurrence in medication-related necrosis of the jaw. Here, ampicillin/sulbactam may be superior to clindamycin [35, 36].

For clean-contaminated oncological interventions, antiinfectious therapy for 24 h only was shown effective in five reviews and 1 retrospective study [37–42]. In contrast, one retrospective study and one controlled clinical trial found prolonged therapy protective against SSI [7, 43]. In cases of microvascular free-flap reconstruction, a 3–5-day regime might reduce SSI [38, 44]. Here, clindamycin seems not suitable to prevent SSI [45]. For parotid gland surgery, single shot prophylaxis with cefazolin is sufficient to reduce SSI [46]. However, infection rates after flap and graft dermatological procedures on the nose and ear did not differ

significantly between patients received single shot prophylaxis vs. placebo [47].

Nineteen studies were found evaluating perioperative prophylaxis in third molar removal with low to high risk of bias. The use of prophylactic antibiotics did not significantly reduce SSI in nine clinical trials [48–56] and two retrospective analyses [57, 58]. Three meta-analyses concluded no support of routine prescription for healthy people undergoing third molar removal [59–61]. In contrast, two clinical trials showed SSI significantly higher where no antibiotics were administrated [62, 63] and three reviews found systemic antibiotics efficient in reducing dry socket and SSI significantly [64–66]. One clinical trial showed no justification for antibiotics performing intra-alveolar dental extraction [67].

For dental implants, five studies with low risk of bias demonstrate that perioperative antibiotic as a single shot prophylaxis before placement might reduce dental implant failure but not SSI [68–72]. However, single shot prophylaxis may be beneficial in preventing postoperative pain [73]. One retrospective study with high risk of bias found antibiotics for 7 days effective in implant survival [74] In other studies with low risk of bias, no statistically significant differences between single shot prophylaxis and prolonged postoperative course were found [72, 75–77]. If

Table 2 Results of the literature search are summarized in order of the investigated surgical procedure

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Tan et al. 2011 [10]	Meta-analysis	SSI	Orthognathic surgery	4 articles compared the period of prophylactic antibiotic usage, and 1 compared the infection prevention effect of different types of antibiotics with placebo	Single dose versus placebo: (600 mg clindamycin i.v. 15 min before surgical incision Vs. Saline solution intravenously every 6 h for 24 h) Reduced infection rate found in the antibiotic group (RR 0.27, 95% CI 0.11–0.68) Single dose versus single day (1 g ampicillin i.v. at induction and 500 mg ampicillin i.v. every 6 h for 24 h vs. Placebo): no difference (RR 3.00, 95% CI 0.83–10.79) short term (1.2 g amoxicillin–clavulanic acid intravenously 30 min before surgery and every 8 h during operation and 1.2 g amoxicillin–clavulanic acid intravenously 8 h after surgery versus long-term (625 mg amoxicillin–clavulanic acid tablet orally every 8 h after surgery for 5 d): no difference (RR 1.33, 95% CI 0.31–5.67)	Low	Ia

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Danda et al. 2011 [12]	Meta-analysis	SSI	Orthognathic surgery	Antibiotic prophylaxis Penicillin G 2 µg i.v./ amoxicillin 1 mg i.v. at induction or clindamycin 300 mg at induction and every 3 h perioperatively/ penicillin G 2 µg i.v. at induction and every 2 h perioperatively/ cefpiramide 1 g i.v. 30 min preoperatively with short-term (penicillin G 2 µg 3 h postoperatively/ clindamycin 600 mg intravenously every 6 h for 24 h/Ampicillin 500 mg intravenously every 6 h for 24 h) vs. extended-term postoperative antibiotics (cefpiramide 1 g intravenously 2×/day for 3 days/amoxicillin–clavulanate 625 mg orally every 8 h for 5 days/amoxicillin 500 mg every 8 h or clindamycin 150 mg every 6 h for 5 days)	Difference in rates of infection between the 2 groups was found to be statistically significant ($p < 0.01$)	Very low	Ia
Danda et al. 2010 [13]	RCT	SSI	Orthognathic surgery	Ampicillin 1 g i.v. at induction with group 1 (single dose) placebo vs group 2 (single day) ampicillin 500 mg intravenously every 6 h for 24 h	Difference in rates of infection in both groups was of interest but not statistically significant ($p > 0.05$)	Moderate	Ib

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Oomens et al. 2014 [11]	Review	SSI	Orthognathic surgery	Preoperative antibiotics vs. no antibiotics vs. prolonged postoperative (amoxicillin–clavulanate 2200 mg i.v. 30 min preoperatively OR cefuroxime 1500 mg i.v. 30 min preoperatively/antibiotics Clindamycin 600 mg i.v. 15 min preoperatively and 3 times daily for 24 h Ampicillin 1 g i.v. (at induction and 4 times daily for 2 days) + amoxicillin 500 mg oral (3 times daily for 3 days) (ampicillin 1 g i.v. (at induction) + amoxicillin 500 mg oral (3 times daily for 5 days)	Preoperative antibiotic prophylaxis appears to be effective. No evidence of the effectiveness of (continuous) postoperative administration was found	Low	Ia

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Brignardello_Petersen et al. 2015 [14]	Meta-Analysis	SSI	Orthognathic surgery	Preoperative vs. short-term (amoxicillin 1 g i.v. at induction, followed by 500 mg i.v. 3 h postoperatively/ampicillin 500 mg intravenously every 6 h for 24 h and ampicillin 1 g intravenously at induction/.0 g of a third-generation cephalosporin (cefpiramide) i.v. 30 min before surgery/single dose of 600 mg clindamycin and saline solution intravenously 15 min before surgery) vs. long-term (amoxicillin 500 mg orally every 8 h for 5 days/1.0 g of Cefpiramide 30 min before surgery, as well as twice daily until 3 days after surgery/625-mg tablet amoxicillin–clavulanic acid orally every 8 h postoperatively for 5 days	Long-term antibiotic prophylaxis probably reduces the risk of SSI; moderate-quality evidence. There is uncertainty surrounding the relative effects of short-term antibiotics compared with a single dose; low-quality evidence	Very low	Ia
Davis et al. 2016 [15]	Retrospective analysis	SSI	Orthognathic surgery	Cefazolin 1/2 g 30 min before surgery, followed by 3 postoperative doses every 8 h vs. clindamycin 600 mg 30 min before surgery, followed by 3 postoperative doses every 8 h vs. penicillin G 2 Mio U 30 min before surgery, followed by 4 doses every 6 h	Prophylactic use of cefazolin appears to be more effective than penicillin and clindamycin for preventing SSIs in orthognathic surgery. The benefit of extending prophylactic antibiotics beyond 48 h must be closely investigated	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Davis et al. 2017 [17]	RCT	SSI	Orthognathic surgery	Perioperative prophylaxis with 1 day vs. 3 day postoperative antibiotics (IV cefazolin 2 g before incision; in patients allergic to cefazolin, IV clindamycin 600 mg was administered. All patients received 3 postoperative IV doses of cefazolin 1 g every 8 h or clindamycin 600 mg every 8 h. After completion of the IV antibiotics, group A received oral liquid cephalexin 500 mg or clindamycin 300 mg 4 times daily for 2 days, and group B received a flavored oral liquid placebo 4 times daily for 2 days)	Three days of postoperative cefazolin and cephalexin markedly decreases SSI rates compared with 1 day. However, with the number needed to treat of 10	Low	Ib
Naimi-Akbar et al. 2018 [18]	Review	SSI	Orthognathic surgery	Single shot vs Placebo (600 mg i.v. clindamycin 15 min prior to surgery and 600 mg i.v. clindamycin 6 hourly for 24 h postoperatively vs i.v. placebo solution 6 hourly for 24 h postoperatively)	With respect to antibiotic prophylaxis in orthognathic surgery, most of the studies to date have been poorly conducted and reported. Thus scientific uncertainty remains as to the preferred antibiotic and the optimal duration of administration	Very low	Ia

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Posnick et al. 2017 [16]	Retrospective analysis	SSI	Orthognathic surgery	I.v. prophylactic antibiotics 15 to 30 min before the surgical incision with cefazolin 1 g/2 g. Postoperative doses were given intravenously every 8 h until hospital discharge. This was followed by an additional course of cephalexin (500 mg every 6 h, elixir form) extending for a 5-day total antibiotic regimen. Patients with a history of penicillin allergy were given clindamycin 600 mg	Incidence of SSI was limited to 1% of patients who were given cefazolin or cephalexin extended for 5 days	High	III
Wahab et al. 2013 [3]	RCT	SSI	Bilateral sagittal split osteotomy	Amoxycillin 1.0 g intravenously at induction with (a) two postoperative doses of saline solution i.v. four hourly vs (b) two postoperative doses of 500 mg amoxycillin i.v. four hourly	There was a statistical difference in the rates of infection between the two groups ($p = 0.04$). The findings indicate that a short postoperative course of antibiotics is more effective than a single preoperative dose	High	Ib
Schaefer et al. 2013 [29]	Retrospective analysis	SSI	Open reduction internal fixation of mandible fractures	Perioperative antibiotics with various regime (ampicillin/sulbactam, clindamycin, cefazolin, cefazolin/clindamycin, levofloxacin, cefazolin/ampicillin/sulbactam, ceftazidime/clindamycin, vancomycin, and vancomycin/ciprofloxacin/clindamycin)	The infection rate with ampicillin/sulbactam was 0%, whereas the infection rate for clindamycin was 19.35%	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Schaller et al. 2013 [20]	RCT	SSI	Mandibular fractures	Prophylactic amoxicillin/clavulanic acid 1.2 g i.v. 1-1-1 with (a) 5-day amoxicillin/clavulanic acid 625 mg 1-1-1 p.o. or (b) 5-day placebo 1-1-1 p.o	A 1-day postoperative course of antibiotic is as effective in preventing infective complications as a 5-day regimen	Low	Ib
Morris et al. 2014 [19]	Meta-analysis	SSI	Facial fracture	Antibiotic prophylaxis (cefazolin, ceftriaxone, and penicillin, cofluampicillin) vs. no antibiotic	Current evidence supports the use of prophylactic antibiotics in mandibular fractures, probably from the time of injury until the completion of the perioperative course, with no additional benefit of postoperative antibiotic prophylaxis	Low	IIa
Mottini et al. 2014 [21]	Retrospective analysis	SSI	Facial fracture	Amoxicillin/clavulanic acid 1.2 g intravenously every 8 h and (a) 1 day of postoperative antibiotics vs. (b) five or more days of postoperative antibiotics	no significant difference in the incidence of infection between the groups receiving postoperative antibiotics for 1 day versus 5 days or more ($p = 0.77$)	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Knepil et al. 2010 [86]	Clinical audit	SSI	Zygomatic fracture	No antibiotics vs. different perioperative antibiotics regime (cefuroxime 750 mg induction and 2 post-operative doses. cefuroxime 750 mg and metronidazole 500 mg, at induction and 2 post-operative doses vs. augmentin 1.2 g induction and 2 post-operative doses. augmentin 1.2 g, at induction and 2 post-operative doses vs. co-fluampicillin 250/250 induction and 2 post-operative doses. Co-fluampicillin 250/250 mg and metronidazole 500 mg, at induction and 2 post-operative doses	Low incidence of infection following surgery for fractures of the zygoma and wide variation in the prescription of prophylactic antibiotics	High	IV
Hindawi et al. 2011 [88]	Retrospective analysis	SSI	Mandibular fractures	None vs. perioperative antibiotics (a) Systemic (b) Intraoral (c) Topical (because of the variability in prescribed antibiotics, there was insufficient statistical power to assess any relationship among specific antibiotics used, infection, and type of injury)	No significant differences between infected and noninfected individuals with regard to administration of preoperative antibiotics (risk ratio, 1.899)	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Lauder et al. 2010 [22]	Retrospective analysis	SSI	Midface and frontal sinus trauma	(a) Pre- (> 2 h before surgery) and perioperative (2 h before surgery) antibiotic treatment vs. (b) perioperative antibiotic treatment vs. (c) peri- and postoperative antibiotic treatment vs. (d) pre-, peri- and postoperative antibiotic treatment of different regimes (not further defined)	no significant difference ($p = 0.248$) between infection rates for patients in each antibiotic group (preoperative, postoperative, pre- and postoperative, only perioperative	High	III
Mercuri 2012 [1]	Review	SSI	Temperomandibular total joint replacement	Antibiotic prophylaxis (cefazolin, clindamycin, cephalosporin, or penicillin-based antibiotics in the perioperative period and continued their use for a mean of 7 days (range 5 to 14) postoperatively) vs. no antibiotics	Antibiotic prophylaxis within 1 h before surgical incision is important in decreasing the incidence of SSI in orthopedic TJR	High	IIb
Soong et al. 2014 [23]	RCT	SSI	Midfacial fractures	Prophylactic amoxicillin/clavulanic acid 1.2 g i.v. 1-1-1 with (a) 5-day amoxicillin/clavulanic acid 625 mg 1-1-1 p.o. or (b) 5-day placebo 1-1-1 p.o	A 1-day postoperative course of antibiotic is as effective in preventing infective complications as a 5-day regimen	Low	Ib
Adalarasan et al. 2010 [30]	Retrospective analysis	SSI	Maxillofacial fracture	Placebo vs perioperative antibiotic with (a) penicillin 5 mio units i.v. or (b) cefotaxime 2 g i.v. 30 min before surgery	Infection rates were found to be not statistically significant (p values for groups 1, 2, and 3: 0.71, 0.85,0.43)	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Campos et al. 2015 [25]	RCT	SSI	Maxillofacial fracture	Perioperative antibiotic prophylaxis (2 g of cefazolin) plus no antibiotics vs. 1 g of cefazolin every 6 h for 24 h	No statistically significant differences in the efficacies of the two regimens; for mandible fracture alone, extended antibiotics proved to be more efficacious ($p = 0.02$)	Moderate	Ib
Gaal et al. 2016 [24]	Retrospective analysis	SSI	Mandible fracture	(1) Intraoperative and preoperative (prescribed at the time of initial consultation of injury before operative management) antibiotic administration, (2) intraoperative and postoperative (prescribed to be taken immediately after operative management) antibiotic administration, and (3) intraoperative, preoperative, and postoperative antibiotic administration (amoxicillin, amoxicillin+clavulanate (augmentin), clindamycin, cephalexin (keflex), penicillin, ampicillin+sulbactam (unasyn), clindamycin, piperacillin+tazobactam (zosyn), cefazolin)	Limiting antibiotic exposure to only intraoperative antibiotic prophylaxis in patients undergoing transoral operative treatment of isolated open mandibular fractures was not associated with an increased risk of SSIs	High	III
Habib et al. 2018 [26]	Review and meta-analysis	SSI	Maxillofacial fracture	Efficacy of pre-, peri-, and postoperative antibiotic prophylaxis (various regime)	No significant difference, also no differences for mandibular fractures or open surgical techniques	Low	Ia

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Hammond et al. 2017 [27]	Retrospective analysis	SSI	Maxillofacial fractures	Regimen 1 = amoxicillin/clavulanicacid (augmentin) 1.2 g intravenously three times daily before operation, followed by 625 mg orally three times daily for 5 days postoperatively Regimen 2 = augmentin 1.2 g intravenously three times daily before operation and for two doses postoperatively, followed by 625 mg orally three times daily for 5 days. Regimen 3 = Metronidazole 500 mg intravenously three times daily before operation, followed by 400 mg orally three times daily for 5 days postoperatively Regimen 4 = Metronidazole 500 mg intravenously three times daily before operation and for two dose postoperatively, followed by 400 mg orally three times daily for 5 days	No significant difference in complication rate, no differences between the regimens	High	III
Huang et al. 2015 [31]	Retrospective analysis	SSI	Orbitozygomatical fractures	Prophylactic intravenous ampicillin with metronidazole and continued for 24 h postoperatively	With a nil infection rate at the RBWH, future studies should focus on whether the use of prophylactic antibiotics is appropriate	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Perepa et al. 2018 [28]	RCT	SSI	Mandible fractures indicated for open reduction and rigid internal fixation	Amoxicillin with clavulanic acid and metronidazole pre-operatively and 1 day course of IV antibiotics (amoxicillin with clavulanic acid 1.2 gm and metronidazole 500 mg) and 4 day course of oral antibiotics (amoxicillin with clavulanic acid 625 mg and Metronidazole 400 mg) vs. 1 day course of IV antibiotics (amoxicillin with clavulanic acid 1.2 g and metronidazole 500 mg) postoperatively	No significant benefit in administration of 5 days regimen or 1 day regimen of antibiotics in patients undergoing open reduction and internal fixation for isolated fractures of mandible	Low/moderate	Ib
Aznar et al. 2015 [32]	RCT	SSI (postoperative fistula)	Clef palate surgery	Single shot prophylaxis with cefuroxime (30 mg/kg) with (a) 5-day regimen of oral amoxicillin (50 mg/kg/day) vs. (b) placebo	Fistulas were noted in 17.1 percent in the placebo group and in 10.7 percent in the antibiotic group ($p = 0.085$)	Low	Ib
Rottgers et al. 2016 [33]	Retrospective analysis and questionnaire	SSI	Primary palatoplasty	Single preoperative dose alone vs. course of postoperative antibiotics vs. preoperative dose and some duration of postoperative antibiotics vs. no antibiotics [agents:Penicillin (5.2%), first-generation cephalosporin (64.2%) Unasyn (12.6%)]	Study group recommends a single preoperative dose of ampicillin/sulbactam. Current evidence cannot justify the use of protracted antibiotic regimens	High	III/IV
Schonmeyr et al. 2015 [34]	Retrospective analysis	Short term surgical complications	Primary cleft lip repair	Single intraoperative dose of cefuroxime (30 mg/kg)	The incidence of wound infection can be kept relatively low, even without the use of postoperative antibiotics	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Marghalani et al. 2014 [59]	Meta-analysis	SSI	Third molar removal	Antibiotic prophylaxis vs. no antibiotics (regimens not specified)	The authors did not support routine prescription of antibiotic prophylaxis for healthy people undergoing extraction of third molars	Very low	Ia
Lee et al. 2014 [48]	Retrospective analysis	SSI	Third molar removal	No antibiotics vs. Perioperative antibiotics with cefditoren pivoxil (100 mg orally 3 times a day for 1 week)	In cases grouped by similar class of difficulty, there was no significant correlation between antibiotic prophylaxis and postoperative complications ("easy" group $p = 1.00$; "moderate" group $p = 1.00$; and "difficult" group $p = 0.65$)	High	III
Lopez-Cedrun et al. 2011 [62]	RCT	SSI	Third molar removal	1: amoxicillin 500 mg (total 2 g) 2 h before surgery and 15 tablets of placebo to be taken 3 times daily for 5 days 2: placebo 2 h preoperatively and 15 tablets of placebo taken 3 times daily for 5 days 3: placebo preoperatively and 15 tablets of amoxicillin 500 mg to be taken immediately after surgery 3 times daily for 5 days	Postoperative infections were significantly correlated to placebo group ($p = 0.001$)	Low	Ib
Iglesias-Martin et al. 2014 [49]	CCT	SSI	Third molar removal	Amoxicillin and clavunate 875/125 mg every 8 h for 7 days vs. amoxicillin 1 g every 8 h for 7 days	No statistically significant differences ($p > 0.05$) were found	Moderate/high	IIa

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Arteagoitia et al. 2015 [50]	RCT	SSI	Lower third molar removal	Placebo vs. 2 g amoxicillin/125 mg clavulanic acid i.v. 2 h before surgery and postoperatively twice a day for 4 days	The difference of infection rate was not statistically significant ($p = 0.278$)	Low	Ib
Arteagoitia et al. 2016 [64]	Review and meta-analysis	SSI	Lower third molar removal	Efficacy of prophylactic amoxicillin with or without clavulanic acid in reducing the incidence of dry socket and/or infection after third molar extraction	Amoxicillin with clavulanic acid reduces dry socket significantly, but the routine prescription of amoxicillin with or without clavulanic acid is not justified	Very low	Ia
Pasupathy et al. 2011 [53]	RCT	SSI	Third molar removal	Placebo vs. (a) Amoxicillin 1 g orally 1 h before surgery and (b) metronidazole 800 mg orally 1 h before surgery	SWI is 36% lower in amoxicillin group compared with the placebo group but not statistically significant ($p = 0.067$)	Low	Ib
Xue et al. 2015 [52]	RCT	SSI	Removal of impacted mandibular third molars	Amoxicillin 0.5 g 1 h preoperatively, or clindamycin hydrochloride 0.3 g vs. placeobo	Prophylactic amoxicillin (or clindamycin) is not effective for the prevention or reduction of postoperative inflammatory complications	Low	Ib
Bezerra et al. 2011 [51]	RCT	SSI	Third molar removal	Two 500 mg capsules of amoxicillin vs. placebo	Use of prophylactic antibiotics did not significantly reduce the presence of associated inflammatory/infectious events	Low	Ib
Cho et al. 2017 [61]	Review	SSI	Third molar removal	Postoperative antibiotics (regimen not defined)	Corticosteroids and antibiotics should only be used in selected cases	Moderate	IIb
Isiordia-Espinoza et al. 2015 [60]	Review and meta-analysis	SSI	Third molar removal	Amoxicillin compared with no treatment or placebo	Amoxicillin given prophylactically or postoperatively does not reduce the risk of infection in healthy patient	Very low	Ia

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Lang et al. 2017 [63]	CCT	SSI or alveolar osteitis	Third molar removal	Antibiotic use of any type (penicillin, amoxicillin, clindamycin, erythromycin, tetracycline, or other antibiotic), categorized as yes or no	Results of this study suggest that antibiotic therapy, regardless of type, dose, frequency, or pattern of delivery, is associated with a decreased risk of inflammatory complications after M3 removal	Moderate/high	IIb
Prajapati et al. 2016 [57]	Retrospective analysis	SSI	Third molar removal	No antibiotics	None of the patients showed any of the signs or symptoms of infection	High	III
Ramos et al. 2016 [65]	Review and meta analysis	SSI	Third molar removal	Systemixc antibiotics (penicillin group, doxycycline, clindamycin, metronidazole) vs. placebo	Overall-RR was 0.43 (95% confidence interval [CI] 0.33–0.56; $p < 0.0001$); number needed to treat, 14 (95% CI 11–19), Systemic antibiotics significantly reduce the risk of dry socket and infection	Very low	Ia
Reiland et al. 2017 [58]	Retrospective analysis	SSI or alveolar osteitis	Third molar removal	Amoxicillin post-operative oral (PO) antibiotics vs. cefazolin perioperative intravenous (IV) antibiotics	No significant differences	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Martin-Ares et al. 2017 [54]	RCT	Non-infectious clinical symptoms	Third molar removal	750 mg amoxicillin orally every 8 h for 5 days post-operative vs. placebo	Antibiotic treatment had a slight beneficial effect on inflammation, and a greater effect on post-operative pain, which lead to a reduction in analgesic consumption. However, the prolonged administration of antibiotics had no real medical indications to justify their use and can cause serious health problems in the long term	High	
Marcussen et al. 2016 [66]	Review	SSI or alveolar osteitis	Third molar removal	Single dose of pre-operative antibiotic administered perorally, intravenously, intramuscularly, or topically	A single oral dose of 2 g of amoxicillin before lower third molar osteotomy surgical extraction significantly decreased the incidence of SSI. A single dose of 0.8 g of penicillin V before lower third molar osteotomy surgical extraction significantly decreased the incidence of alveolar osteitis	Low	Ib
Milani et al. 2015 [56]	RCT	Mouth opening, facial edema and pain	Third molar removal	(G1), amoxicillin (1 g) 1 h before surgery + 500 mg 8/8 h for 7 days; group 2 (G2), 1-g amoxicillin 1 h before surgery plus placebo, with identical appearance to G1, 8/8 h for 7 days; and group 3 (G3), placebo 1 h before surgery and 500 mg 8/8 h for 7 days	There was no difference among groups with respect to any of the parameters evaluated ($p > 0.05$)	Low	Ib

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Sayd et al. 2018 [55]	CCT	SSI	Third molar removal	Amoxicillin–clavulanic acid with metronidazole administered three times daily vs. azithromycin administered once daily and with metronidazole 400 mg three times daily	There was no difference among groups	High	IIa
Sidana et al. 2017 [67]	RCT	SSI	Intra-alveolar dental extraction	No antibiotics vs. antibiotics for 3 days (amoxicillin 500 mg) vs. a single dose of antibiotic (amoxicillin 500 mg) 1 h before the extraction procedure with no postoperative antibiotics, vs. mouthwash and no antibiotics	No justification for routine antibiotic prophylaxis for dental extractions in healthy patients	Low	Ib
Hoefert et al. 2011 [36]	Retrospective analysis	SSI (relapse)	BPNOJ	Short-term oral antibiotic treatment up to 1 week vs. long-term treatment of different regimes (ampicillin sulbactam (sultamicillin), amoxicillin, clindamycin, cefaclor, cefazolin cefuroxime cefotaxime ciprofloxacin levofloxacin moxifloxacin doxycycline metronidazole)	Surgical treatment in combination with a longterm preoperative antibiotic treatment can lead to a complete healing ($p < 0.05$)	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Zirk et al. 2017 [35]	Retrospective analysis	SSI (relapse)	MRONJ	Ampicillin/sulbactam (3.3 g) or clindamycin (3.600 mg). When patients were discharged from hospital they continued to take antibiotics until wound healing was completed	Perioperative antibiotic regime for patients with MRONJ stage II and III undergoing surgically treatment does have an influence on the recurrence of the disease. Clindamycin should no longer be considered a viable option for the initial perioperative antibiotic treatment, but piperacillin/tazobactam	High	III
Cachovan et al. 2011 [80]	RCT	SSI (patients' perceived pain)	Odontogenic abscesses and infiltrates	400 mg moxifloxacin p.o. once daily vs. 300 mg clindamycin p.o. four times daily for 5 days consecutively	In patients with inflammatory infiltrates, moxifloxacin was significantly ($p = 0.003$) more effective in reducing pain at days 2 to 3 of therapy than clindamycin. No significant differences between groups were found for patients with odontogenic abscesses	Low	Ib
Gomez-Arambula et al. 2015 [81]	RCT	Hospitalization length	Odontogenic maxillofacial infectious processes	Moxifloxacin, 400 mg IV once daily until infection remission, vs. Clindamycin 600 mg IV every 6 h plus Ceftriaxone 1 g IV two times daily	Mean hospitalization time in days showed no significant difference in both groups	Moderate	Ib
Sharaf et al. 2011 [72]	Review	SSI and implant failure	Dental implant	Single preoperative dose vs. single preoperative dose and multiday postoperative therapy of different regimens vs. no antibiotic therapy	Single dose of preoperative antibiotic therapy may slightly decrease the failure rate of dental implant	Low	IIb

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Chrcanovic et al. 2014 [70]	Meta-analysis	SSI and implant failure	Dental implant	Placebo *vs.* perioperative antibiotics (different regimes)	Use of antibiotics significantly affected the implant failure rates ($p = 0.0002$). No significant effects on post-operative infections ($p = 0.520$)	Very low	Ia
Krasny et al. 2016 [74]	Retrospective analysis	Implant failure	Dental implant	Antibiotics twice a day for 7 days and reconstruction procedure before implantation vs. No surgical procedures before implantation. (Under amoxicillin protection 3093 implants were placed and under clindamycin and cephalosporin protection the total of 216 implants)	Perioperative use of antibiotic therapy beneficially influences tissue healing, provides safety and success of the surgical procedure, as well as translates into high efficacy of implantation (99.52%)	High	III
Carcuac et al. 2016 [78]	RCT	Probing pocket depth (PPD), gingival inflammation (BOP), intra-oral radiographs	Surgical treatment of peri-implantitis	Systemic antibiotics/implant surface decontamination with an antiseptic agent vs. systemic antibiotics/implant surface decontamination with saline vs. no systemic antibiotics/implant surface decontamination with an antiseptic agent vs. no systemic antibiotics/implant surface decontamination with saline (regimens not defined)	While adjunctive systemic antibiotics had no impact on treatment success at implants with a nonmodified surface, a positive effect on treatment success was observed at implants with a modified surface. The likelihood for treatment success using adjunctive systemic antibiotics in patients with implants with a modified surface, however, was low	Low	Ia

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Hallstrom et al. 2017 [79]	RCT	Probing pocket depth (PPD), gingival inflammation (BOP), intraoral radiographs	Open flap debridement of peri-implantitis	Zithromax® 250 mg × 2 at the day of surgery, and 250 mg × 1 per day during four additional days vs. no antibiotics	Surgical treatment of peri-implantitis with adjunctive systemic azithromycin did not provide 1-year clinical benefits in comparison with those only receiving open flap debridement	Not blinded	Ib
El-Kholey et al. 2014 [75]	RCT	SSI	Dental implant	Single dose of 1 g p.o. amoxicillin with (a) placebo vs. (b) 500 mg amoxicillin postoperatively every 8 h for 3 days	No statistically significant differences between the two antibiotic regimens ($p=1.0$)	Low	Ib
Esposito et al. 2013 [69]	Meta-analysis	SSI and implant failure	Dental implant	Various prophylactic antibiotic regimens versus no antibiotics	Higher number of implant failures in the placebo group ($p=0.2$)	Very low	Ia
Nolan et al. 2014 [73]	RCT	SSI (postoperative morbidity)	Dental implant	3 g amoxicillin 1 h pre-operatively, and 28 patients (control group) received placebo capsules 1 h pre-operatively	No significant differences were found for most of the signs of post-operative morbidity 2 and 7 days postoperatively. Except for pain ($p=0.01$) and interference with daily activities ($p=0.01$)	Low	Ib
Ata-Ali et al. 2014 [68]	Meta-analysis	SSI and implant failure	Dental implant	Placebo vs Amoxicillin 2 g i.v. 1 h preoperatively	Antibiotic treatment reduce the risk of implant failure statistically significant ($p=0.003$), but not the risk of SSI ($p=0.754$)	Low	Ia
Park et al. 2018 [76]	Review	Prosthesis failure, implant failure, adverse events or postoperative complications	Dental implant	Antibiotics in dental implant therapy (multiple different regimens)	Antibiotic use in healthy patients for the prophylaxis of surgical infection associated with dental implant placement does not appear to improve clinical outcomes	Low	IIb

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Lund et al. 2015 [71]	Review and meta-analysis	Implant survival	Dental implant	Antibiotics in dental implant therapy (amoxicillin in different administrations)	Antibiotic prophylaxis in conjunction with implant placement gives a modest reduction by 2% of the risk for implant loss. However, the sub-analysis of the primary studies suggests that there is no benefit of antibiotic prophylaxis in uncomplicated implant surgery in healthy patient	Low	Ia
Ata-Ali et al. 2014 [68]	Meta-analysis	SSI and implant failure	Dental implant	Placebo vs Amoxicillin 2 g i.v. 1 h preoperatively	Antibiotic treatment reduce the risk of implant failure statistically significant ($p = 0.003$), but not the risk of SSI ($p = 0.754$)	Low	Ia
Arduino et al. 2015 [77]	RCT	Prosthetic and implant failures, adverse events and early postoperative complications	Dental implant	Single preoperative dose (2 g of amoxicillin orally) vs. an additional 2-day postoperative course of oral amoxicillin (in addition with 1 g the evening of the day of surgery and 1 g twice a day for 2 days following surgery)	No statistically significant differences were observed	Low	Ib
Waasdorp et al. 2010 [84]	Review	SSI (implant failure)	Immediate implant placement of dental implants into fresh extraction sockets	Different protocols prior to immediate implant placement to prevent infection	Evidence suggests using an antibiotic when immediately placing implants into infected site	Low	IIb
Rosengren et al. 2018 [47]	RCT	SSI	Flap and graft dermatological closures on the nose and ear	Single oral preoperative 2 g dose of cephalexin vs. placebo	No difference in wound infection rates between patients who received perioperative antibiotic therapy and those who did not	Low	Ib

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Shkedy et al. 2016 [46]	Retrospective analysis	SSI	Parotid gland surgery	Cefazolin i.v., the first dose in the operating room and then every 8 h for a period of 24 to 48 h vs. no antibiotics	A single oral 2 g dose of cephalexin given before complex skin closure on the nose and ear reduced SSI	High	
Koshkareva et al. 2014 [37]	Review	SSI	Oncological head and neck surgery	Choice and duration of a perioperative antibiotic prophylaxis regimen in adult oncologic head and neck surgery summary (clindamycin–gentamicin, cefoperazone cefotaxime, cefazolin, clindamycin ampicillin–sulbactam)	Antimicrobial prophylaxis is not indicated in clean head and neck cases, but is indicated for patients undergoing clean-contaminated surgery	Low	Ia
Kruse et al. 2010 [38]	Review	Survival rate	Microvascular free-flap reconstruction for cancer of the head and neck	Antibiotics in microsurgery	Amoxicillin 2 g and clavulanate potassium 0.2 g i.v. for 5 days is sufficient	Low	IIb
Man et al. 2011 [40]	Retrospective analysis	SSI	Uncontaminated Neck Dissection	No prophylactic antibiotics vs. (a) intraoperative antibiotics vs. (c) intra- and postoperative antibiotics (cefazolin was given in 177 cases, clindamycin was given in 29 cases, ampicillin/sulbactam was given in 22 cases, vancomycin was given in two cases, ampicillin was given in one case, and piperacillin/tazobactam was given in one case	The development of a wound infection was not associated with antibiotic regime	High	III
Vila et al. 2017 [41]	Review and meta-analysis	SSI	Clean-contaminated resection for head and neck cancer	Different antibiotics regimen in head and neck oncology	No difference in the risk of wound infections between patients receiving 1 day vs 5 days of systemic antibiotic prophylaxis	Low	Ia

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Cannon et al. 2017 [42]	Review	SSI	Clean-contaminated head and neck oncology	Different antibiotics regimen in head and neck oncology	For clean-contaminated surgical procedures, prophylactic antibiotics are required and the evidence suggests that clindamycin alone is not sufficient	Low	Ia/IIb
Langerman et al. 2016 [89]	Retrospective analysis	SSI	Clean-contaminated head and neck surgery	Antibiotics on the day of surgery (DOS) vs DOS and first postoperative day (ampicillin/sulbactam clindamycin cefazolin 1 metronidazole cefazolin and other)	Prolonging ampicillin/sulbactam beyond the day of surgery may have a protective effect against SSI	High	III
Veve et al. 2017 [44]	Review	SSI	Head and neck cancer free-tissue transfer	Antibiotics in head and neck oncology (different regimens)	Short durations (e.g. less than 3 days) of broad-spectrum antibiotics that cover Gram-positive, Gram-negative, and anaerobic organisms (e.g. ceftriaxone plus metronidazole or ampicillin/sulbactam) are recommended	Low/moderate	Ia/IIb
Murphy et al. 2017 [44]	Retrospective analysis	SSI	Clean- and-contaminated head and neck osteomyocutaneous free flap	Antibiotics in head and neck oncology with osteomyocutaneous free flap (ampicillin + sulbactam, clindamycin, cefazolin and other)	Clindamycin antibiotic was strongly associated with the development of an SSI, with 50% of that cohort developing a recipient SSI (odds ratio = 7.0; $p < 0.002$), regardless of duration of use. The rate of development of a recipient SSI with cefazolin was 25% and that with ampicillin plus sulbactam was 19%	High	III

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Russell et al. 2012 [39]	Review	SSI	Clean-contaminated oncologic surgery	Perioperative antibiotics of different regimes vs. no antibiotics	Antibiotic prophylaxis is effective when used in clean-contaminated oncologic surgery and administered prior to the start of surgery. Importantly, there is no evidence to support the use of antibiotic prophylaxis beyond 24 h postoperatively	Low	IIb
			Maxillofacial surgery	Single shot prophylaxis vs. peri- and prolonged antibiotics	In patients undergoing maxillofacial surgery, a strict perioperative antibiotic regime seems to be sufficient for prophylaxis against surgical site infections	High	
Bartella et al. 2017 [43]	CCT	SSI	Major oncological head and neck surgery	Combined peri and postoperative antibiotic prophylaxis (1.5 g or 3 g ampicillin (2 g) p sulbactam (1 g). In the case of a known allergic reaction to penicillin-derived antibiotics, clindamycin 600 mg was used in the same fashion) until the fifth postoperative day vs. only perioperative antibiotic prophylaxis vs. perioperative antibiotic therapy and enhanced measures of local antiseptic care of the surgical wounds and the tracheostoma	Significant decrease in surgical site infections in major head and neck cancer surgery by application of a post-operative antibiotic prophylaxis regimen	High	IIa

Table 2 (continued)

Refs.	Study type	Parameter	Intervention	Comparison	Outcome	Risk of bias	Evidence level
Bartella et al. 2018 [82]	CCT	SSI	Maxillofacial surgery	Single shot prophylaxis vs. peri- and prolonged antibiotics (ampicillin/sulbactam, cefuroxim, co-trimoxacol)	In patients undergoing maxillofacial surgery, a strict perioperative antibiotic regime seems to be sufficient for prophylaxis against surgical site infections	Moderate/high	IIa

Evidence level refers to recommendations of the Cochrane library

peri-implantitis occurs, adjunctive antibiotics to surgical treatment showed no improved outcome [78, 79].

In treatment of odontogenic abscesses and inflammatory infiltrates, moxifloxacin was found to reduce pain more effective that clindamycin, but mean hospitalization time showed no significant differences in both groups [80, 81]. One study was found that evaluated the benefit of single shot prophylaxis vs. prolonged antibiotics in maxillofacial surgical interventions in general [82].

Discussion

In this study, recommendations for the perioperative antibiotic prophylaxis in case of maxillofacial surgery within the scope of the systematic literature search for the planned german S3 guideline "antibiotic prophylaxis in surgery" are reported. In general, SSI depends on patient-related risk factors, among them poor nutritional status, smoking, diabetes and impaired immune system. Other significant variables for wound infection, for example, in oncology are tumor stage, previous chemotherapy, duration of preoperative hospital stay, permanent tracheotomy, and presence of laryngeal and hypopharyngeal cancer [38]. In addition, rates of antibiotic resistance are increasing and directly related to the proportion of the population that receives antibiotics, and the total antibiotic exposure. Thus, increased antibiotic use leads to more resistance [4]. In this context, organisms such as various streptococci (aerobic and an-aerobic species), other oral anaerobes including *Bacteroides* species, *Peptostreptococcus* species, *Prevotella* species, *Fusobacterium* species, *Veillonella* species, Enterobacteriaceae, and staphylococci are pathogens of special interest that may lead to antibiotic resistance. Here, up to 95% remain susceptible to metronidazole and co-amoxiclav, but penicillin alone can no longer be relied upon [4].

Also, procedure-related risk factors summarized in the classification of the surgery (clean, clean-contaminated, contaminated, dirty) alter infection rate. As postoperative surgical site infections occur in < 1% of patients undergoing clean head and neck operations, antibiotic prophylaxis is not thought to be beneficial [37]. On the other hand, use of antibiotic prophylaxis in cases of clean-contaminated facial surgery has been well established [22]. Since the intraoral mucosa is exposed to oropharyngeal secretion, saliva, and bacteria, incidence of infections in clean-contaminated head and neck surgery without preoperative antibiotics has been reported at 30–80% [38]. Perioperative antibiotic prophylaxis is, therefore, of fundamental importance in maxillofacial surgery. Here, some studies suggest that short-term antibiotic therapy might increase the number of resistances. However, when short-term (24 h) antibiotics is compared with longer-term (5 days) prophylaxis following excision

of head and neck lesions, significantly fewer patients were found with wounds infected by MRSA in the short-term group. This is why SIGN guidelines and others recommend the duration of prophylactic antibiotic therapy as single dose except in special circumstances such as prolonged surgery or major blood loss [4].

To improve implementation and methodological standard, an upgrade of the existing S1 guideline to an consensus-decided S3 guideline for antibiotic prophylaxis in surgery was initiated by the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF, register number 067/009) and 25 collaborated medical societies.

Dentoalveolar surgery

In dentoalveolar surgery, literature is ambivalent for antibiotic therapy. One major point of interest was third molar removal. Overall, there is evidence that use of prophylactic antibiotics cannot significantly reduce the presence of surgical site infections [48–56, 60]. Given the low risk of infection versus potential development of resistant bacteria and management of infection, there is no evidence to support routine prescription of antibiotic prophylaxis for healthy people undergoing extraction of third molars [54, 59, 61]. Even in anatomically difficult cases measured with the difficulty index described by Pederson et al, there were no significant associations between antibiotic prophylaxis and postoperative complications although a small but insignificant increase in the number of dry sockets and infections was observed [48]. Only two trials (one retrospective analysis with high risk of bias included) could be found where postoperative infections were correlated significantly with placebo group [62, 63]. Furthermore, antibiotics may be used to prevent dry alveolar sockets and therefore reduce postoperative morbidity [64–66]. Nevertheless, the number needed to treat was considerably high with low prevalence of infection and lack of serious complications in placebo groups. The authors, therefore, conclude that the routine prescription of antibiotics is not justified [64]. If perioperative antibiotic therapy is indicated in special circumstances, amoxicillin is similar efficacious in preventing infection as amoxicillin and clavulanate but reduces gastrointestinal side effects [49]. Furthermore, there were no differences between amoxicillin with or without clavulanic acid and clindamycin [52], cefazolin [58], metronidazole [53] or azithromycin and metronidazole [55] in preventing SSI. Therefore, no recommendation in favor of a specific substance can be given.

Overall, there is good quality of evidence not to support the perioperative antibiotic therapy in healthy patients. No evidence could be obtained that evaluated potential benefits and associated harms of perioperative antibiotics for patients with pre-existing conditions. However, patients at a higher risk of infection are more likely to benefit from prophylactic antibiotics, because infections in this group are likely to be more frequent, associated with complications and be more difficult to treat [83].

For dental implants, antibiotics that are discussed intended not only to decrease postoperative infection rate but also to reduce implant failure. To minimize implant failure, there are concerns associated with the widespread use of antibiotics, since adverse events may occur [68]. Among the results provided in this study, a Cochrane review sums up evidence that not only antibiotics are beneficial for reducing implant failure placed in ordinary conditions but also it is still not clear whether postoperative antibiotics are beneficial and which regime is the most effective [69]. Furthermore, when dental implants should be placed immediately after tooth extraction in infected sites of chronic periapical infections, antibiotic prophylaxis seems indicated [84]. This is consistent with the EAO (European Association of Osseointegration) consensus that in "complex" cases (for example, immediate placement in extraction sockets and/or a compromised patient), a beneficial effect of antibiotic prophylaxis cannot be excluded but is not recommended in "straightforward" implant surgery in uncompromised patients [85]. Single shot prophylaxis, for example, with Amoxicillin 2 g i.v. or orally 1 h preoperatively, might reduce implant failure [68, 69, 72] and prevent postoperative pain [73], but no significant effects on post-operative infections could be found [70, 73, 75]. Besides one retrospective study with high risk of bias, no difference between single shot and prolonged therapy was found [74, 76, 77]. From the obtained data, no recommendation of a specific drug class can be given, since a variety of different regimens were used. However, most studies preferred amoxicillin or other aminopenicillins [71, 77]. No RCT could be found that directly compared the different substances. In a retrospective analysis, there was no difference between amoxicillin, clindamycin or cephalosporin in implant failure [74]. A complex systematic review by Lund et al, therefore, conclude that "antibiotic prophylaxis might reduce the risk for implant loss by 2% but sub-analysis of the primary studies suggests that there is no benefit of antibiotic prophylaxis in uncomplicated implant surgery in healthy patient" [71]. Overall, there is good quality of evidence that perioperative antibiotic as a single shot prophylaxis before placement can reduce dental implant failure, not SSI, and might be suitable only in complex cases. If peri-implantitis occurs, adjunctive antibiotics to surgical treatment showed no improved outcome in comparison to open flap debridement alone [78, 79].

It is known that antibiotics are an important component in the conservative treatment strategy and an essential adjunct for odontogenic infections with primarily surgical treatment [80]. For dentoalveolar surgery in infected sites,

different regime of preoperative antibiotics before abscess/infiltrate incision and duration of antibiotics before revision of drug-related osteonecrosis of the jaw within the scope of anti-resorptive therapy were analyzed. As an adjunctive therapy for patients with odontogenic abscesses, moxifloxacin was at least as effective as clindamycin with regard to pain reduction, clinical outcome, and safety but mean hospitalization time showed no significant differences in both groups [80, 81]. For medication-related osteonecrosis of the jaw (MRONJ) a long-term antibiotic treatment may lead to a complete healing and therefore reduce postoperative infections and disease recurrence. Here, ampicillin/sulbactam may be superior to clindamycin [35, 36]. Altogether, evidence is of poor quality. Therefore, no recommendations could be derived.

Maxillofacial surgery

The efficacy of perioperative prophylactic antibiotics in preventing postoperative wound infections after clean-contaminated head and neck surgery where the aerodigestive tract is violated has been clearly established in clinical trials [40, 86]. There was no need for prolonged antibiotic therapy, but risk factors as tracheotomy were associated with higher risk for SSI [82]. In orthognathic surgery, postoperative infection rates vary from 1.4 to 33.4% but use of antibiotics remains controversial [12]. In this study, good quality of evidence that preoperative antibiotic prophylaxis appears to be effective in reducing the postoperative infection rate in orthognathic surgery could be presented [10, 11]. Since orthognathic surgery is mainly performed in young, healthy adults without significant comorbidities, a single-dose antibiotic regimen is effective in preventing SSI [10, 13]. Some reviews were found that evaluate extended antibiotic therapy with conflicting results. Danda et al. found prolonged antibiotics to be more effective in decreasing the risk of postoperative wound infection [12]. In case of bilateral sagittal split osteotomy, a short postoperative course of antibiotics is more effective than a single preoperative dose [3]. In addition, a Cochrane review concluded that there is moderate-quality evidence for SSI risk reduction with long-term antibiotic prophylaxis [14]. Conversely, Oomens et al. conclude that additional continuous postoperative antibiotics are not beneficial [11]. Moreover, Tan et al. reviewed application for extended postoperative period is not recommended [10]. As for the specific substance, cefazolin and aminopenicillins were used the most in the variety of regimens. Studies with high risk of bias evaluated cefazolin to be more effective than penicillin and clindamycin when antibiotic therapy is recommended [15, 16] but the relatively high number to treat (up to 10) lead to uncertainty with respect to the preferred compound and optimal range of prophylaxis [17, 18]. Taken together, preoperative antibiotics in orthognathic surgery is

recommended with a good quality of evidence but benefit of prolonged therapy and which regime is the most effective remain uncertain.

In maxillofacial traumatology, facial fractures vary in location and severity and can span the range of wound classifications including clean, clean contaminated, contaminated, and dirty/infected [19]. Frequently, contamination of the surgical wounds with the bacterial flora of the oral cavity and sinuses occurs. Therefore, these procedures are considered clean-contaminated wounds and hence are at an increased risk of postoperative wound infection. In general, prophylactic antibiotics are both justified and widely used [23, 29]. However, it is still not clear whether a postoperative course of an antibiotic reduces the risk of infection, and if so to what extent [20]. Consequently, good quality of evidence that supports perioperative antibiotic prophylaxis for mandibular and Lefort-1/2 fractures was found [19, 20, 23]. Additionally, a 1-day postoperative course of antibiotic was effective in preventing infective complications but no additional benefit of postoperative antibiotic prophylaxis could be found [19, 21, 24, 26–28]. Since the infection rate was nil in orbitozygomatical fractures, a study questions the use of antibiotics in this indication [31]. In contrast, for temporomandibular joint replacement, perioperative prophylaxis is efficient in reducing SSI [87]. Only poor quality of evidence in terms of retrospective analyses or other studies with a high risk of bias was obtained that found no significantly differences between different regimes (amoxicillin with and without clavulanic acid, cefazolin, clindamycin, cefotaxime and piperacillin + tazobactam) [21, 22, 30, 86, 88]. Therefore, extended postoperative antibiotic regimes cannot be recommended.

For cleft lip, alveolus and palate surgery only scarce evidence could be perceived. Primary efficiency endpoint was occurrence of postoperative fistulas. Here, antibiotic prophylaxis as single shot or 5-day regime failed to show reduction of statistically significance [32, 33]. In addition, incidence of wound infections was low even without the use of postoperative antibiotics [34]. Up to date, antibiotic prophylaxis cannot be recommended.

The duration of perioperative antibiotics in clean-contaminated oncologic head and neck surgery has been investigated extensively. In general, prophylaxis should be administered to high-risk patients, for example, with complex congenital cyanotic disease [37]. The incidence of infections without preoperative antibiotics has been reported at 30–80%; therefore, perioperative antibiotic prophylaxis is indicated for patients undergoing clean-contaminated surgery such as reconstructive surgery in case of head and neck cancer [37–42]. The available regimens include clindamycin (600 mg every 6 h), ampicillin–sulbactam (1.5 or 3 g every 6 h), amoxicillin–clavulanate (2 g every 8 h), or cefazolin (2 g every 8 h) [37, 45]. There was no RCT that

directly compared different substances with each other to prevent SSI. However, there is limited evidence for duration of perioperative antimicrobial prophylaxis that exceed 24 h [37, 39, 89]. Only one retrospective study with high risk of bias and one controlled clinical trial found prolonged therapy protective against SSI [7, 43]. A possible indication for prolonged therapy may be seen in microvascular free-flap reconstruction with conflicting results whether perioperative prophylaxis or a 3–5-day regime is more effective in reducing SSI [38, 44]. In clean head and neck surgery, antimicrobial prophylaxis is not indicated [37, 40]. For parotid gland surgery, single shot prophylaxis with cefazolin is sufficient to reduce SSI [46] but not indicated in flap and graft dermatological reconstruction of nose and ear [47]. Taken together, there is good quality of evidence that antibiotic prophylaxis is recommended in clean-contaminated, not in clean major oncological procedures of the head and neck. Prophylaxis is recommended for 24 h only with conflicting results in cases of free-vascular flap transfer.

Conclusions

In this review, current evidence for antibiotic prophylaxis of oral and maxillofacial surgery was summarized that was obtained within the scope of the systematically literature search for the planned German S3 guideline "antibiotic prophylaxis in surgery". The respective studies were evaluated and level of evidence as well as risk of bias according to the Cochrane Library is highlighted. As major results, prophylactic perioperative antibiotics might reduce SSI in major procedures such as clean-contaminated oncological head and neck surgery, but not in clean procedures of the head and neck and prophylaxis is of benefit for 24 h only. In orthognathic surgery, preoperative antibiotics can reduce SSI with a good quality of evidence but benefit of prolonged therapy and which regime is the most effective remains uncertain. In traumatology, perioperative antibiotic prophylaxis for mandibular and Lefort-1/2 fractures might reduce SSI, but extended postoperative antibiotic regimes longer than 24 h cannot.

For dentoalveolar surgery, evidence is more ambivalent. For dental implants, perioperative antibiotic as a single shot prophylaxis before placement might reduce dental implant failure but not SSI. For third molar removal, perioperative antibiotic therapy is of uncertain benefit for healthy patients, but no evidence could be obtained that evaluated antibiotic therapy for patients with pre-existing conditions. Overall, a multitude of different regimes were administered regardless of the respective surgical procedure.

In summary, consensus process of the planned S3 guideline is much in need to transfer especially the indecisive results for antibiotic prophylaxis in dentoalveolar surgery in clinical praxis and encourage adherence to guidelines.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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