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**A literature review of perioperative antibiotic administration in surgery for medication-related
osteonecrosis of the jaw**

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Abstract

Purpose Few studies exist that focus on the details of perioperative antibiotic administration for surgery to treat medication-related osteonecrosis of the jaw (MRONJ). The regime and duration of perioperative antibiotics applied in published studies were reviewed to clarify appropriate perioperative antibiotic use in MRONJ surgery.

Methods A literature search was conducted using the MEDLINE database via PubMed.

Results The search resulted in 453 hits on PubMed. After reading the downloaded full-text, 17 articles met the inclusion and exclusion criteria. The most common perioperative antibiotic used for MRONJ surgery was a combination of penicillin-based antibiotics and β -lactamase inhibitor (52.9%), and the second most common regime was penicillin-based antibiotics with metronidazole (17.6%). The duration of administration was 2 weeks postoperatively in nine studies, whereas four studies applied long-term administration (2–6 weeks postoperatively).

Conclusions Oral and maxillofacial surgeons mostly prefer penicillin-based antibiotics plus β -lactamase inhibitor or metronidazole for MRONJ surgery. The duration of administration of these medications may be based on empirical experience.

Keywords: medication-related osteonecrosis of the jaw, surgery, perioperative antibiotic, duration, bacterial sampling

Introduction

The definition of medication-related osteonecrosis of the jaw (MRONJ) is (1) current or previous treatment with antiresorptive or antiangiogenic agents; (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks; and (3) no history of radiation therapy to the jaw or obvious metastatic disease in the jaw [1,2]. The position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) divided MRONJ into four stages [1]. In stage 0 (patients with no clinical evidence of necrotic bone, but with clinical and radiographic findings), antibiotic use is recommended for control of infection. In stage I, antibiotic therapy is not mentioned because stage I patients are asymptomatic and have no evidence of infection. In stage II (symptomatic patients with necrotic bone and evidence of infection), the antibiotic regime should be adjusted according to the results of the microbial culture. Most isolated microbes are sensitive to the penicillin group, and quinolones, metronidazole, clindamycin, doxycycline and erythromycin have been used for patients with penicillin allergy [1]. In stage III (e.g., patients with pathologic fracture or an orocutaneous fistula), debridement in combination with antibiotic therapy is recommended. In brief, antibiotic therapy for MRONJ serves two purposes: (1) infection control to reduce inflammation in symptomatic patients, and (2) perioperative administration. Although there are no evidence-based specific recommendations about the type of antibiotic or the duration of administration for MRONJ treatment, the Japanese Allied Committee on Osteonecrosis of the Jaw does not recommend long-term administration of antibacterial agents, given the risk of acquired drug resistance [3].

Few studies exist that focus on the type and duration of perioperative antibiotic administration in MRONJ surgery. We collected and investigated the details of perioperative antibiotic regimes applied in published articles, especially focusing on the duration of administration. The methods of collecting samples for bacterial identification applied in previous studies were also

1 reviewed, because the identification of causative bacterial species is so important. Finally, this
2 literature review aimed to discuss the appropriate perioperative antibiotic regime for MRONJ surgery.
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7 **Methods**

8 **Search strategy and selection criteria**

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10 In December 2017, a MEDLINE search was performed via PubMed using the following combination
11 of key terms as shown in Figure 1. The articles that were identified had to meet the following
12 inclusion criteria: human studies; studies including MRONJ patients who underwent treatment
13 (conservative and invasive); explicit description of the antibiotic regime administered for MRONJ
14 treatment; and studies published in English. This review also includes studies that provide explicit
15 descriptions of sample collecting for bacteriological examination in MRONJ patients. The following
16 exclusion criteria were applied: in vitro and animal studies; studies focusing on risk factors (e.g.,
17 where the study population consisted of patients who received antiresorptive agents and underwent
18 dental extraction); case reports; case series studies with small sample sizes, and studies including only
19 conservative treatment as shown in Figure 1.
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38 **Results**

39 **Literature review**

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41 The search resulted in 453 hits on PubMed. The downloaded full-text articles were read, and 24
42 articles met the inclusion criteria. Seventeen articles were selected to evaluate perioperative antibiotic
43 regimes and seven were selected to evaluate bacterial sampling methods (Figure 1).
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53 **Perioperative antibiotic regimes for MRONJ surgery**

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55 Table 1 shows a summary of the perioperative antibiotic regimes applied in each study. The most
56 common antibiotic was a combination of penicillin-based antibiotics (ampicillin or amoxicillin) and
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1 β -lactamase inhibitor (sulbactam or clavulanate) that was used in nine out of the 17 studies (52.9%)
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3 [4–12]. The reported doses of ampicillin/sulbactam were 4.5–9 g/day [5,6]. The durations were 1 day
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5 preoperatively and 5–14 days postoperatively [4,6,7,9,10]. The second most common regime was
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7 penicillin or amoxicillin with metronidazole [13–15]. The durations were 3–7 days preoperatively and
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9 and 1–3 weeks postoperatively [13,14]. Two studies used penicillin-based antibiotics alone for 2
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11 weeks postoperatively [16,17]. Clindamycin (600 mg $\times$ 3/day) was used for penicillin allergic patients
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13 in all studies using penicillin, except for one study in which oral azithromycin (1 g/day) was used
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15 [16]. Other studies used a doxycycline-based regime [18,19] or carbapenem [20]. The longest
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17 duration of postoperative antibiotic administration was moxifloxacin or amoxicillin with clavulanate
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19 for 4–6 weeks after surgery [18].
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24 Of the 17 studies, three aimed to evaluate the efficacy of fluorescence-guided surgery
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26 [4,13,19], two of which were from the same author group [4,19]. Mouth rinsing with chlorhexidine
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28 was encouraged at concentrations of 0.02% [17], 0.12% [6,7,12,20], 0.2% [13], and 2% [16]. One
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30 study used hexetidine mouth rinse [10]. In three studies, nasogastric feeding tubes were used
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32 postoperatively [6,7,10]. One study did not permit subjects to use overlying dentures for 12 weeks
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34 postoperatively, and required them to follow a liquid diet for 2 weeks postoperatively followed by a
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36 soft diet [14].
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41 One study reported that there was no statistical difference in surgical outcome related to the
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43 duration of intravenous perioperative antibiotic administration: complete healing (median 8; range 4–
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45 12 days), relative healing (median 8; range 5–10 days), and no healing (median 8; range 5–11 days)
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47 [6]. Except for studies that did not mention the detailed duration of postoperative antibiotic
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49 administration, the duration of postoperative antibiotic administration was under 14 days in most
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51 studies included in this literature review [4,6,7,9,10,13,15,16,20], whereas the duration was long-term
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53 (2–6 weeks) in only four studies [14,17–19]. Two studies administered long-term penicillin-based
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antibiotics for cases positive for actinomyces (4–6 weeks) [7,12]. One study mentioned that postoperative antibiotics were administered until wound healing was complete [5].

Postoperative healing rates in these studies were 27.6–100% [4-7,9-20]; however, the evaluation of timing and the definition of outcomes were different in each study. In the group in which postoperative antibiotics were administered for under 14 days, the median healing rate was 85.9% (range, 27.6–100%), and in the group in which long-term postoperative antibiotics were administered, the median healing rate was 94.4% (range, 27–100%).

Methods of sampling and microorganism identification

Table 2 shows a summary of the sampling methods and microorganism identification applied in each of the seven studies. In three studies (42.9%), bone was collected for bacterial identification during resection surgery or sequestrectomy [21–23]. In one study, bone biopsies were retrieved from the center of the necrotic bone, as well as from visually healthy bone, with special care taken not to contaminate the biopsy areas before, during, or after sampling [21]. This study indicated the flow of microorganisms through the bone texture, because the microflora detected in the peripheral zone of the lesion (visually healthy bone) were the same as those inside the necrotic lesions, and consisted mainly of anaerobic bacteria, representative of periodontal microflora [21]. In three other studies, soft tissues were collected for microorganism analysis [5,24,25]. Soft tissue samples were associated with the necrotic bone [24,25] and the periodontium [24]. In one study, the soft tissues surrounding the lesions were collected during the surgery to investigate submucosal infections [5]. Only one study used a smear technique for microorganism analysis [10].

In five of the seven studies, polymerase chain reaction (PCR) was used to identify microorganisms [21–25], and one study targeted only actinomyces [22]. Three studies applying PCR were from the same author group [23–25]. In three studies, a traditional culture method was used for bacterial identification [5,10,22].

Discussion

This literature review investigated the perioperative antibiotic regimes in each study to suggest the appropriate antibiotic use for MRONJ surgery. Surprisingly, only 17 studies described the details of the perioperative antibiotic regimes. Some studies lacked information about the type of perioperative antibiotic or the duration of administration [26–31]. For example, one study mentioned the duration of perioperative antibiotic administration (at least 5 days after surgery), but not the type [27], and was therefore excluded. In some studies, the antibiotic regimes were not unified [29,30]. One study in which the antibiotic regime was unified (2–10 weeks sitafloxacin) had fewer than 30 cases that underwent surgery, and was therefore excluded [32]. Existing guidelines on antibiotic prophylaxis in surgery uniformly recommend stopping prophylaxis 24 hours after wound closure [33,34]. A recent meta-analysis established that there is no difference in the risk of wound infection with 1 day versus 5 days of systemic antibiotic prophylaxis in clean-contaminated head and neck surgery, consistent with existing guidelines [35]. One of the reasons for conducting the current literature review was to establish whether oral and maxillofacial surgeons regard perioperative antibiotics in MRONJ surgery as prophylactic or therapeutic administration.

A previous systematic review concluded that a surgical approach to MRONJ lesions seems to be the most effective in every disease stage [36]. Recent large sample size studies including 361 [28] and 325 [37] subjects concluded that extensive surgical treatment may be more beneficial than conservative surgery. The success of the surgery depends on the radical nature of the operation, and a sparing bone resection sometimes results in the development of refractory MRONJ [11]. However, most patients with advanced MRONJ are often in a tumor-bearing state and are being treated with an antiresorptive agent for metastatic disease. Therefore, it is necessary to carefully ascertain whether a radical procedure will improve the patient's quality of life [6]. The aims of MRONJ surgery are to relieve soft tissue irritation, provide pain relief, and achieve infection control [5] but, in some cases,

the aim is not to completely eliminate necrotic regions. In cases in which segmental resection is avoided, the necrotic regions may remain after surgery. Experienced oral and maxillofacial surgeons know that bone bleeding is sometimes not apparent, as advanced bone sclerosis can occur in stage III [5] and occasionally even in stage II MRONJ. In 2004, Ruggiero et al. [38] noted that it is often difficult to obtain a surgical margin with viable bleeding bone. Regions of necrotic bone that are a source of infection and are not reactive to local irrigation and antibiotic therapy should be removed, but the margin of the debridement will remain exposed [38]. Therefore, the concept of downstaging (i.e., MRONJ stage II or III to asymptomatic stage I [6]) is important, especially in patients with advanced MRONJ who are in a tumor-bearing state. When downstaging, not only the amount of bone resection but also the perioperative antimicrobial treatment may have an impact on the maintenance of asymptomatic MRONJ [5].

The fact that this literature review found that all the included studies administered antibiotics for longer than recommended by the existing guideline (i.e., only 24 hours administration after wound closure) suggests that some oral and maxillofacial surgeons may consider perioperative antibiotic administration to be a part of therapy rather than prophylaxis alone. However, this literature review could not clarify whether the duration of postoperative antibiotic administration affects surgical outcome (i.e., the recurrence of MRONJ). Only one study by Bodem et al. [6] reported that the duration of postoperative antibiotic administration was not significantly different among patients showing complete healing after surgery, relative healing, and no healing (the median duration in all categories was 8 days postoperatively). A study by Hoefert et al. [30] compared groups of patients who received a short-term preoperative antibiotic regime (1–8 days before surgery) and a long-term regime (23–54 days before surgery). After surgery, various types of antibiotic were given for a median period of 7 days intravenously and for another 10–12 days orally. They found that the success rate was higher after prolonged preoperative antibiotic therapy (complete healing rate: long-term 70–87% and short-term 35–53%) [30]. A retrospective longitudinal cohort study including 77 MRONJ

1 patients reported that the mean duration of antibiotic treatment was 405.6 ± 405.9 days (63.6% of
2 patients underwent surgery) [39]. Regular antibiotic administration can increase resistance to
3 antibiotics [40]. This literature review cannot determine which long-term or short-term duration of
4 postoperative antibiotics have a positive effect on surgical outcomes in MRONJ patients. It may be
5 necessary to refer to guidelines for diseases in other regions of the body. For example, the Infectious
6 Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic
7 foot infections stated that the most appropriate duration of therapy for diabetic foot infections is not
8 well defined, but it is important to consider the presence and amount of residual dead and infected
9 bone and the state of the soft tissues [41]. When a radical resection leaves no remaining infected
10 tissue, only a short duration of antibiotic therapy (specifically, 2–5 days) is needed. In contrast, if
11 infected or dead bone remains despite surgery, prolonged treatment is recommended (residual
12 infection requires treatment for 4–6 weeks; residual dead bone requires treatment for more than
13 3 months) [41]. Although diabetic foot infections and MRONJ are not the same disease, it seems that
14 the concept of changing the duration of perioperative antibiotic administration depending on the
15 extent of residual necrotic bone after surgery may be applicable to MRONJ surgery.

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17 A study by Zirk et al. [5] reported that cultured bacteria isolated from submucosal lesions
18 were significantly more susceptible to ampicillin/sulbactam (79.1%) than to clindamycin (44.9%), and
19 patients being treated with ampicillin/sulbactam were significantly less likely to require a second
20 intervention than the clindamycin group. They noted the relevance of applying an empirical antibiotic
21 regime. Another recent systematic review and meta-analysis indicates that head and neck free flap
22 cases receiving clindamycin prophylaxis have an increased likelihood of recipient site infection
23 compared to ampicillin/sulbactam, because patients with head and neck squamous cell carcinoma of
24 the upper aerodigestive tract harbor increased levels of intraoral gram-negative bacteria for which
25 clindamycin is not sufficient [42]. It is likely that most of the microorganisms isolated from MRONJ
26 lesions are sensitive to penicillin [43]. Penicillin is the most frequently used antibiotic as a first-choice

for odontogenic infections [44], and the addition of β -lactamase inhibitor is still controversial. This literature review cannot determine which type of perioperative antibiotic regime is most suitable for MRONJ surgery, but it does reveal that current oral and maxillofacial surgeons prefer penicillin-based antibiotics plus β -lactamase inhibitor or metronidazole (70.6%, 12/17 studies) rather than penicillin alone or other regimes. Based on the results of the microorganism analysis in the seven studies shown in Table 2, the authors consider that treatment with penicillin-based antibiotics is sufficient for MRONJ surgery. One contentious issue is whether β -lactamase inhibitor should be added. Hallmer et al. [21] concluded that necrotic bone lesions in MRONJ contain mainly anaerobic bacteria, representative of periodontal microflora. A previous study noted that β -lactamase-positive subgingival bacterial species were present in more than half of the study subjects with severe chronic periodontitis [45]. Although two studies administered doxycycline preoperatively [18,19], a recent prospective trial showed that only 50% of oral pathogens found in odontogenic infections were susceptible to doxycycline [46]. The susceptibilities to other antibiotics are as follows: 98% to moxifloxacin, 96% to amoxicillin-clavulanic acid, 85% to levofloxacin, 67% to penicillin, and 60% to clindamycin [46]. Since carbapenem resistance is an ongoing public-health problem of global dimensions [47,48], routine use of carbapenem for perioperative antibiotic in MRONJ surgery is not recommended. Taking these studies into account, the authors consider that a combination of penicillin-based antibiotics and β -lactamase inhibitor is a reasonable treatment for MRONJ surgery. However, Ji et al. [25] noted that there were differences in the bacterial populations between patients taking systemic antibiotics and a non-antibiotic cohort with no prior antibiotic therapy. Abuse of antibiotics should be avoided.

This literature review has several major limitations. First, this study aimed to survey the important studies in the published literature, but all relevant studies may not have been identified. The study populations, purposes, and definitions of surgical outcomes in the included articles were heterogeneous. This review excluded studies in which details of the antibiotic regime were described,

1 but which included only cases that underwent conservative therapy. We did not conduct a meta-
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3 analysis because of the heterogeneity of the literature results. Regardless of these limitations, our
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5 literature review highlights an underestimated but important issue. We hope that a guideline for
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7 appropriate antibiotic use for MRONJ surgery will be established in the future.
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10 11 12 **Conclusions**

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14 This literature review reveals that the most common regime for perioperative antibiotic administration
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16 for MRONJ surgery is penicillin-based antibiotics plus β -lactamase inhibitor or metronidazole
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18 (70.6%, 12/17 studies). The duration of administration is diverse.
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28 of this manuscript.
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34 **Compliance with ethical standards**

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36 **Conflict of Interest** The authors declare that they have no conflict of interest.
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Figure legend

Figure 1 Study selection.

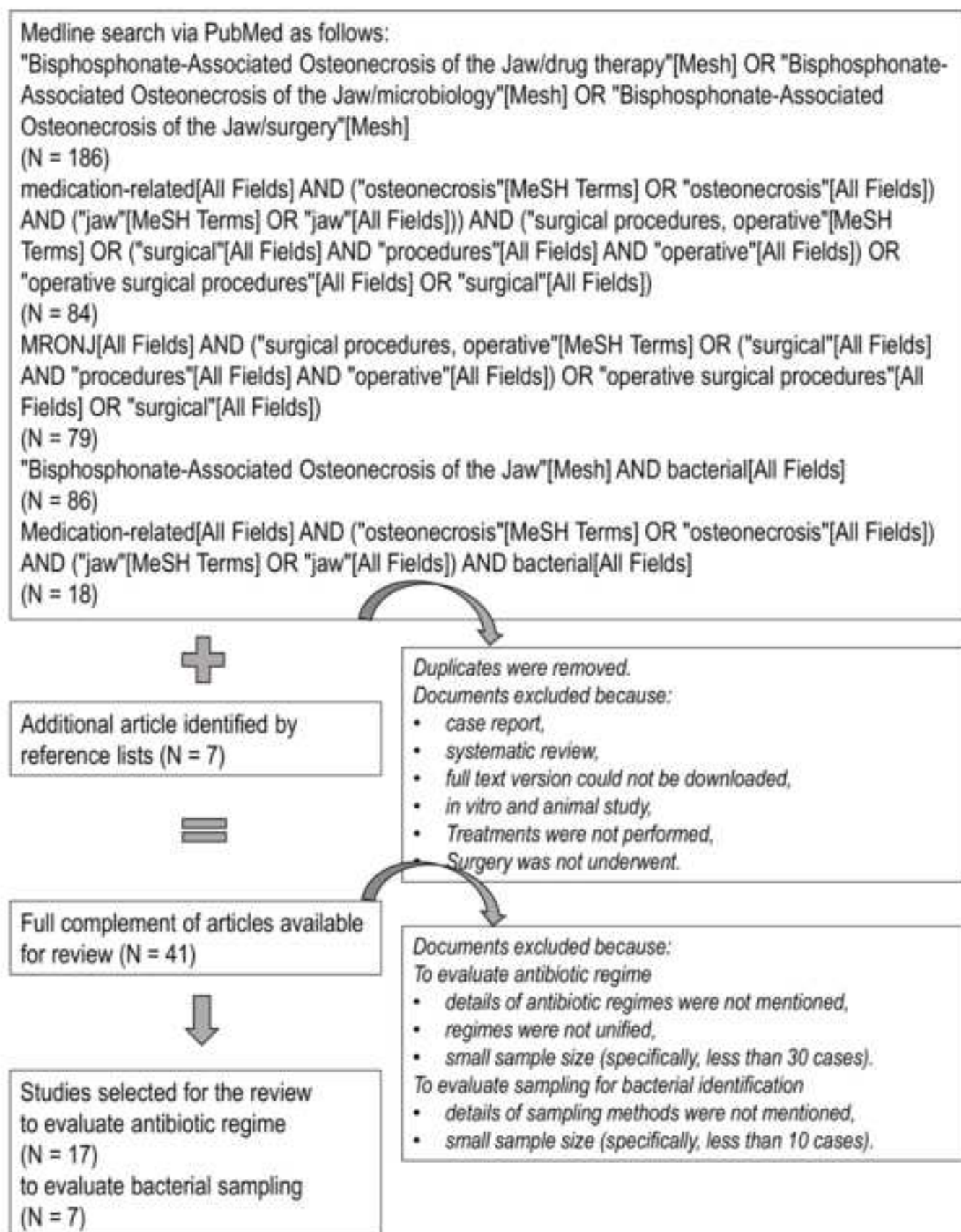


Figure 1

Table 1 Summary of perioperative antibiotic regimes

Types of regime	Reference	<i>n</i> (lesions)	AAOMS stage (%) ^a	Perioperative antibiotic regime	Additional treatment	Definition of outcome	Outcome (%)
Combination of PC-based abx and β-lactamase inhibitor	Ristow et al., 2017 [4]	40 (51)	I 8	Intravenous ampicillin/sulbactam (2 g/1 g) preoperatively	All were TF or AF-guided surgery	8 weeks postoperative: complete mucosal coverage with no exposed bone, infection, or pain	TF 85
			II 80	and 4 days postoperatively			
			III 12	Additional oral abx [regime: NI] for further 6 days			
	Zirk et al., 2017 [5]	143	In TF patients, doxycycline (100 mg × 2) at least 7 days	Ampicillin/sulbactam (3 g × 3) [duration: NI]	Mouth rinse	Local wound healing complete, with no signs of residual mucosal defect or fistula, and no swelling or pain	After 1st intervention, 54.5 did not require second intervention.
				After discharge, patients continue to take abx [regime: NI] until wound healing was completed			
	Bodem et al., 2016 [6]	39 (47)	All were II or III	Intravenous ampicillin/sulbactam (1.5 g × 3) starting at least 1 day preoperatively and 5 days postoperatively	Feeding tube Mouth rinse	12 weeks postoperative: complete mucosal healing or downstaged from stage II or III to asymptomatic stage I	74.5
	Klingelhöffer et al., 2016 [7]	40 (76)	I 44.7	Intravenous amoxicillin/clavulanate starting at least 1 day preoperatively and 10 days postoperatively [dose: NI] [Patient positive for actinomyces (38%) received amoxicillin administration over 4 weeks]	Feeding tube (10 days postoperatively) Mouth rinse	6 months postoperative: complete mucosal healing	Healing 27.6
			II 47.4				
			III 7.9				
	Russmueller et al., 2016 [8]	111	I 39	Amoxicillin (1 g × 2)/clavulanate (500 mg × 2) 4 weeks between admittance and surgery		Early recurrence: exposed bone at operation site during the first 3 months	recurrence 28.9
			II 49				
			III 12				
	Schubert et al.,	54	I 13*	Ampicillin/sulbactam orally 2 days or intravenous 1 day		At least 3 months	I–II 84

	2012 [9]		II 36 III 5	preoperatively [dose: NI] and 10–14 days postoperatively		postoperative: closed soft tissue cover with no symptoms of infection	III 80
	Stockmann et al., 2010 [10]	50	I 26 II 46 III 28	Oral amoxicillin (500 mg × 3)/clavulanate (125 mg × 3) 10 days postoperatively	Feeding tube (10 days postoperatively) Mouth rinse	12 months postoperative: wound healing	89
	Carlson et al., 2009 [11]	82 (95)	I 52.6 II 33.7 III 13.7	Penicillin G for transoral surgery Intravenous ampicillin/sulbactam for transoral/transcutaneous approach during hospital stay	Segmental or marginal resections	Maintenance of mucosal closure with no signs of residual infection or exposed bone [time of evaluation: NI]	91.6
	Wutzl et al., 2008 [12]	41	NI	Amoxicillin (1 g × 2)/clavulanate (500 mg × 3)] during hospital stay [Patient positive for actinomyces (38%) received amoxicillin (1 g × 2) or clavulanate (500 mg × 2) administration 6 months]	Mouth rinse	Mean follow-up 189 (±23) days Intact mucosa and no pain	58.5
Combination of PC-based abx and metronidazole	Giudice et al., 2017 [13]	36 (39)	I 33.3 II 33.3 III 33.3	Amoxicillin (1 g × 2)/metronidazole (250 mg × 3) 3 days preoperatively and 7 days postoperatively	AF-guided surgery Mouth rinse	1 year postoperative: exposure of necrotic bone or infection	Bone exposure: Non-AF 13.3 AF 6.7 Infection: Non-AF 6.7 AF 0
	Pichardo et al., 2016 [14]	74	II 29.7 III 70.3	Intravenous penicillin G/metronidazole 1 week and amoxicillin/metronidazole orally 3 weeks postoperatively	Liquid diet (2 weeks postoperatively)	At least 6 months postoperative: cured (situation with no complaints and presentation of a healed	93.2

						and closed mucosa)	
	Bedogni et al., 2011 [15]	28 (32)	0 31 I 3 II 28 III 38	Ampicillin/sulbactam (1.5 g × 3)/metronidazole (500 mg × 3) intra- and 10 days postoperatively	HBO Segmental resection with reconstruction	6 months recurrence rate of BRONJ	9.4
Only PC-based abx	Nisi et al., 2016 [16]	120 (128)	I 24 II 63 III 13	Amoxicillin/clavulanate (2 g) 2 weeks were used as conservative treatment before surgery Amoxicillin (3 g) preoperatively and (2 g) 2 weeks postoperatively	Mouth rinse	6 months postoperative: good or poor (no change or worse)	Good 84 Poor 16
	Williamson et al., 2010 [17]	40	NI	Amoxicillin (1 g) preoperatively and (500 mg × 3) at least 2 weeks postoperatively	Mouth rinse	Mean follow-up 20 (6–48) months Intact mucosa in surgical area with no signs of infection	100
DOXY-based abx	Fleisher et al., 2016 [18]**	31 (33)	II 94 III 6	Doxycycline 2 weeks preoperatively and moxifloxacin or amoxicillin/clavulanate 4–6 weeks postoperatively	Segmental resection with reconstruction 32% HBO 39%	Mean follow-up 6.6 (2–48) months Healing (mucosal closure with no signs of infection or exposed bone)	Low risk group 100 High risk group 27
	Otto et al., 2016 [19]	54 (65)	0 1.5 I 21.5 II 64.6 III 12.3	Doxycycline (100 mg × 2) starting at least 1 week preoperatively and intravenous Augmentin (2.2 g × 3) or Unacid (3g × 3) 3–5 days postoperatively [Patients with severe infection (mainly stage II and III) metronidazole 500 mg (1-0-1) was added] Additional oral abx [regime: NI] for further 2–4 weeks	Fluorescence-guided surgery	Mean follow-up 12.9 (1–39) months Complete mucosal healing including cases requiring second surgical attempt	94.4
Other regimes	Ferlito et al., 2012 [20]	91	I 8* II or III 83	Intravenous imipenem/cilastatin (500 mg × 2) 2 days preoperatively and 3 days followed by intramuscular piperacillin/tazobactam (2 g × 2) 7 days postoperatively	Conservative surgery for sequestrum Mouth rinse	6 months postoperative: complete healing of soft tissues	100

*Although the staging used in these studies was different from the AAOMS staging (e.g., the scale of the DOESAK [49]), cases were reclassified based on AAOMS staging.

**This study aimed to evaluate the predictive value of fluorodeoxyglucose (FDG) positron emission tomography on postoperative healing outcome, and patients were divided into a low risk group (FDG uptake was restricted superior to the mandibular canal) and a high risk group (FDG uptake was extended inferior to the mandibular canal).

AAOMS = American Association of Oral and Maxillofacial Surgeons, Abx = antibiotics, AF = autofluorescence-guided surgery, DOXY = doxycycline, HBO = hyperbaric oxygen therapy, MRONJ = medication-related osteonecrosis of the jaw, NI = not informed, PC-based abx = Penicillin-based antibiotics, TF = tetracycline fluorescence-guided surgery.

Table 2 Summary of microorganism analysis

Samples	Reference	<i>n</i>	AAOMS stage (%)	Details of sampling	Identification methods	Microorganism identified (%)
Bone	Hallmer et al., 2017 [21]	18	I 5.6 II 94.4	From the center of the necrotic bone and visually healthy bone	PCR	Porphyromonas, Lactobacillus, Tannerella, Prevotella, Actinomyces, Treponema, Streptococcus, Fusobacterium
	Panya et al., 2017 [22]	95	0 1.1 I 15.8 II 62.1 III 21.1	From bone resection surgery	Culture: at least (+2) as positive culture Actinomyces PCR	Culture: Actinomyces 24.2, Mixed oral flora 24.2, p group 20, Streptococci 18.9, Miscellaneous microorganisms 13.6, Candida 9.4, Enterococcus 5.2, Prevotella 5.2 PCR: Actinomyces 96.4
	Wei et al., 2012 [23]	BRONJ 6 Control 6	NI	From sequestrectomy	PCR	BRONJ: Streptococcus 29, Eubacterium 9, Pseudoramibacter 8 Control: Parvimonas 17, Streptococcus 15, Fusobacterium 15
	Zirk et al., 2017 [5]	143	All were II or III	Surrounding soft tissue of submucosal lesion during surgery	Culture	Culture positive: 31.5 Viridans streptococci 22.7, Escherichia coli 12.7, Eikenella corrodens 10, Bacteroides 10, Non viridans streptococci 8.2, Klebsiella 6.4, Prevotella 5.5, Peptococcaceae 3.6, Enterobacter aerogenes/cloacae 3.6, Propionibacterium 1.8, Capnocytophaga 1.8, Staphylococcus aureus 1.8, Others 11.8
	Pushalkar et al., 2014 [24]	MRONJ15 BP 5 Control 10	NI	Soft tissue associated with necrotic bone and periodontium	PCR	BRONJ: Parvimonas 18.3, Fusobacterium 4, Eubacterium 3.1 (exclusive to BRONJ: Xanthomonas 3.8, Lachnospiraceae 2.1, Eubacterium 2.1, Bifidobacterium 2, Bacteroidetes 1.7 BP (BP and periodontal disease): Atopobium 8.7, Rothia 6.3, Pseudoramibacter 4.2, Shuttleworthia 4.2, Afipia 3.1, Bacteroidetes 3.1, Delftia 3.1 Control (periodontal disease): Veillonella 19.7, Peptostreptococcus 8.6, Lactobacillus 7.3, TM7 6.3, Actinomyces 4.4, Mogibacterium 3.9, Porphyromonas 3.6
Soft tissue	Ji et al., 2012 [25]*	Abx 10 Non-abx 10	NI	Soft tissue associated with lesion	PCR	Abx: Firmicutes, Streptococcus intermedius, Lactobacillus gasseri, Mogibacterium timidum, Solobacterium moorei Non-abx: Parvimonas micra, Streptococcus anginosus

Smear	Stockmann et al., 2010 [10]	50	I 26 II 46 III 28	Smear from exposed bone	NI (probably traditional culture)	Actinomyces 54 (66 in bone sample) All microflora were sensitive to amoxicillin with clavulanate as well as clindamycin
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*In this study, antibiotic group patients received tetracycline, doxycycline, ciprofloxacin or amoxicillin for two weeks.

AAOMS = American Association of Oral and Maxillofacial Surgeons, Abx = antibiotics, BP = bisphosphonate, BRONJ = bisphosphonate-related osteonecrosis of the jaw, PCR = polymerase chain reactions, MRONJ = medication-related osteonecrosis of the jaw, NI = not informed.