Alveolar Osteitis Prevention Strategies in Third Molar Extractions

AN EVIDENCE-BASED REVIEW

Community Dentistry DEN207Y DDS2

By: Edwin Chang
Elena Gershenzon
Fotini Papanagiotou
Kevin Kwong
Melanie Tang
Tatjana Semiz
Course Director: Dr. A. Azarpazhooh
Teaching Assistant: Dr. T. Al-Jewair

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University of Toronto
Faculty of Dentistry

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Edwin Chang, Elena Gershenzon, Fotini Papanagiotou, Kevin Kwong, Melanie Tang, and Tatjana Semiz
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Abstract

Introduction: *The management of dry socket, or alveolar osteitis, in dental extractions remains a controversial issue. The goal of this evidence-based review is to systematically review current literature focused on the prevention of AO.* ***Methods:*** *A comprehensive literature search was conducted, and only studies that met our stringent `PICOC` inclusion criteria were included. The selected articles were scored on the `Evidence of efficacy of prevention` checklist and evaluated using the Canadian Task Force Recommendations.* ***Results:*** *Of the 9 articles that met the score cut-off, 5 examined the prevention of dry socket using various antibiotics, 3 examined the prevention of AO using the antiseptic chlorhexidine, and 1 studied the prevention of AO using chlorhexidine alone, and in conjunction with an antibiotic.* ***Discussion:*** *Based on a careful review of literature, it was determined that the administration of systemic antibiotics was inconclusive in preventing AO. However, local administration of antibiotics may provide a preventive effect in the development of AO. Three of the four studies analyzing the effect of chlorhexidine in the prevention of AO demonstrated that chlorhexidine was effective in preventing AO, while one study found chlorhexidine to be effective only when used in conjunction with the systemic antibiotic amoxicillin.* ***Conclusion:*** *There is inconclusive evidence to recommend the use of systemic antibiotics in the prevention of AO; however, evidence supports the use of antiseptics as prophylaxis. Nonetheless, future research with stringent protocols is recommended.*

Key words: dry socket, alveolar osteitis, localized osteitis, post-operative alveolitis, alveolalgia, alveolitis sicca dolorosa, septic socket, necrotic socket, localized osteomyelitis, fibrolytic alveolitis, prevention, management, reduction, third molars, wisdom teeth

Introduction

The term dry socket was first introduced by Crawford in 1896[1]. The condition is self-limiting and typically begins 1-3 days after tooth extraction, with a duration of 5-10 days, before resolving on its own[2,3]. The primary clinical features of dry socket include reports of severe throbbing pain with an extraction socket devoid of clot and/or exposed bone. Marked halitosis, foul taste, and edema of surrounding gingiva with associated regional lymphadenitis are also common[2,3]. Although many terms for dry socket exist (Table 1), the term alveolar osteitis (AO) is most often used in literature; hence, dry socket will be referred to as AO in this paper[4].

AO is the most common complication following the extraction of permanent teeth[4]. The reported incidence ranges from 1-30% in the extraction of third molars[2,5,6], with a 10-fold risk increase in the mandible compared to the maxilla[7]. The symptoms can be debilitating, causing a loss of productivity due to throbbing pain and/or multiple visits to the surgeon's office[2,8]. Although the etiology of AO has not been firmly established, some risk factors of AO include: smoking[9], use of oral contraceptives[10], lack of surgical experience[9,11], poor oral hygiene[11], diabetes[11], and tooth impaction[12].

Currently, two main theories have been proposed for the etiology of AO. Clotting normally occurs via fibrin formation through the enzymatic action of thrombin, which is then degraded through plasmin fibrinolysis[13]. An earlier theory proposed that trauma/infection of the alveolar bone promotes the release of tissue plasminogen activators (tPA), which in turn promotes plasmin formation, fibrinolysis, and the release of bradykinins and kininogenases, mediating pain[14]. However, studies revealed that tPA inhibitors were unable to reduce the incidence of AO, while plasmin inhibitors were successful, suggesting that host tissue tPAs were not responsible for plasmin breakdown in AO[15,16]. Consequent studies on the local application of antibiotics suggested that bacterial products may be responsible for increasing fibrinolysis in AO[2,17,18]. However, further studies are needed to establish a causal relationship.

The majority of interventions for AO focus on prevention rather than treatment. Current preventive measures include antibacterial agents,

antiseptics, antifibrolytics, anti-inflammatory agents, and clot support agents[2]. Numerous studies on these preventive methods are available; however, many reported outcomes have been inconclusive and/or conflicting. Previous systematic reviews generally reported that antibiotics and antiseptic agents appeared to reduce the incidence of AO, whereas alternative methods lacked sufficient data, presented inconsistent results, and/or had more adverse side effects[2,8,12,19-21].

Table 1: List of terms synonymous with dry socket

- Alveolar osteitis
- Localized osteitis
- Postoperative alveolitis
- Alveoalgia
- Alveolitis sicca dolorosa
- Septic socket
- Necrotic socket
- Localized osteomyelitis
- Fibrinolytic alveolitis

There are currently no standard treatments, proposed guidelines, or recommendations regarding AO in North America. However, a national guideline for dental surgery was developed by the Royal College of England in 1997, which recommended prophylactic antibiotics only to those with a history of pericoronitis, an infection due to the impacted tooth, or a compromised immune system[22]. Therefore, it is necessary to conduct a study to systematically review current literature on the prevention of AO. The purpose of this review is to update and reassess the literature on the preventive measures in reducing the incidence of AO by focusing on those with strong study designs.

Methods

Prior to the literature search, inclusion and exclusion criteria were established using the 'PICOC' (population, intervention, control, outcome, and critical appraisal) framework (Table 2). Impacted third molars of both dental arches were included, as the occurrence of AO is most prevalent following third molar extractions[23,24].

Only healthy adults were included in this study; patients with extractions due to infections, patients recently on antibiotics, immune-compromised patients, patients with systemic diseases, and patients with medical conditions that may affect normal blood clotting were excluded from the systematic review, as these populations are at a higher risk of developing AO and typically already require special prophylactic measures[8-12]. However, smokers and patients on oral contraceptives were not excluded from this study even though they are at increased risk for developing AO because these patients normally do not receive additional prophylactic treatment for dental surgery. They also represent such a large percentage of the general population that it would be unjustifiable to exclude them.

Table 2 - Inclusion and exclusion criteria

	Inclusion	Exclusion
P	- Healthy individuals - Adults (≥ 18 years old) - Males and females - Impacted third molars - Mandibular molars	- Extractions due to infections - Patients recently on antibiotics - Immunocompromised - Systemic diseases - Any other medical conditions that can affect blood clotting
I	- Any preventive measure in any form (e.g. antibiotics, antiseptics, antifibrolytics, clot support agents, anti-inflammatories) - Any dosing regimens - Pre and/or post operative treatments	- Post-operative management of AO - Surgical techniques
C	- Placebo - No treatment	
O	- Positive diagnosis of AO: 1. Subjective :Patient report of pain at extracted site within 3 – 7 days post-operation, measured by a visual analogue scale or any other tested and reliable method; AND 2. Clinical: Absence of blood clot and exposed alveolar bone	
C*	- Prospective Randomized Clinical Trials	- Retrospective studies - Pilot studies - Cross sectional studies - Cohort studies - Case reports or series

P- Participant
I- Intervention
C- Control
O- Outcome
C*- Critical appraisal

A comprehensive literature search was conducted electronically for randomized clinical trials (RCTs) published up to and including January 2009 using the electronic databases and keywords listed in figure 1. The search results were further limited by selecting for RCTs conducted on humans that were written in English. Furthermore, a grey literature search was performed via 1) Google scholar, using the previously mentioned keywords, 2) available theses and dissertations, and 3) speaking to faculty members regarding unpublished/current research literature and their professional opinions on the topic.

Figure 1: Flow diagram of search results

Following the search results, the collective articles were manually filtered – by two independent evaluators at each level – for inclusion according to the PICOC criteria at the abstract level, title level, and full-text level accordingly, with an average of 88% agreement between evaluators. The final qualified articles were critically appraised and scored using the "Checklist to Assess Evidence of Efficacy of Therapy or Prevention" adapted from Fletcher[25], with a maximum possible score of 17 (Table 3).

Table 3: Checklist to Assess Evidence of Efficacy of Therapy or Prevention

1.	Was the study ethical?
2.	Was a strong design used to assess efficacy?
3.	Were the outcomes (benefits and harms) validly and reliably measured?
4.	Were interventions validly and reliably measured?
5.	Was the treatment effect large enough to be clinically important?
6.	Was the estimate of the treatment effect beyond chance and relatively precise?
7.	If the findings were "no difference" was the power of the study 80% or better?
8.	Was the assignment of patients to treatments randomized, and were all patients who entered the trial properly accounted for and attributed at its conclusion?
9.	Was loss to follow-up less than 20% and balanced between test and controls?
10.	Were patients analyzed in the groups to which they were randomised?
11.	Was the study of sufficient duration?
12.	Were patients, health workers, and study personnel "blind" to treatment?
13.	Were the groups similar at the start of the trial?
14.	Aside from the experimental intervention, were the groups treated equally?
15.	Was care received outside the study identified and controlled for?
16.	Were all clinically important outcomes considered?
17.	Are the likely benefits of treatment worth the potential harms and costs?

Adapted from: Fletcher, Fletcher and Wagner. Clinical epidemiology – the essentials. 3rd ed. 1996.

The cut-off score for acceptance of an article for systematic review analysis was established to be 9/17 or higher. The cut-off was chosen after determining the minimum number of checklist items essential for a good quality RCT; specifically questions 5 to 15. Any additional checklist items were considered an addition to the quality of the RCT. Finally, the articles that passed the cut-off score were evaluated based on the quality of evidence using the Canadian Task Force Recommendations (CTFRs)[26].

Results

102 results were obtained from the refined search, and 14 additional articles were obtained via grey literature search (Figure 1). After manual evaluation, 39 articles remained for full-text evaluation. 30 articles were rejected after full-text

evaluation, with reasons for exclusion listed in Table 7 (see appendix). The remaining 9 articles were reviewed for their quality using the Checklist to Assess Evidence of Efficacy of Therapy or Prevention. All 9 articles passed the cut-off score, and were subsequently evaluated using the CTFRs (Table 4). Detailed summaries are listed in Tables 5 and 6 (see appendix).

All studies included were RCTs, with one study by Akota et al. using a randomized split-mouth design[27]. Of these studies, five assessed the efficacy of the various antibiotics[27-31] (Table 5), and three assessed the efficacy of the antiseptic chlorhexadine[32-34] in preventing AO (Table 6). One study included a treatment group consisting of both chlorhexidine and the antibiotic amoxicillin[35], and was included in both tables. All but two studies[27,28] provided a placebo comparison group. Each study measured their results within seven days post-operatively. However, both the method(s) of measurement and the diagnostic criteria used to define relevant outcomes varied from study to study. The findings from these studies were mixed.

Antibiotics

The results of the studies that evaluated the use of antibiotics varied. One study demonstrated a statistically significant reduction (p=0.05) in the incidence of post-operative AO with the use of a chlortetracycline-impregnated gauze drain, versus a no-drain treatment[27]. Another study reported a highly significant reduction (p=0.001) in the incidence of AO when oral amoxicillin was used post-operatively in conjunction with chlorhexidine mouth rinse[35]. The other four studies comparing various antibiotics, including clindamycin[30], penicillin[28,29], and metronidazole[31], to their respective control groups, did not achieve statistical significance. It should be noted that dosing regimens varied greatly between these studies. One study was unable to achieve adequate power for detecting significant differences[31], while another study found no cases of AO in both the treatment and control group[29]. The

Table 4: Summary of findings and recommendations

Author, Date	Intervention	Outcome	CTFR
Antibiotics			
Akota et al., 1988	Gauze drain impregnated with chlortetracycline	Significant difference (p=0.02)	B
Ritauz et al., 1992	1000 mg Metronidazole one dose regimen orally pre-operatively	No significant difference (power = 5%)	I
Delilbasi et al., 2002	Chlorhexidine pre-operatively and post-operatively in conjunction with amoxicillin plus clavulanic acid orally	Significant difference (p=0.001)	A
Curran et al., 1974	Penicillin G i.v. followed by 450 mg penicillin orally 4 times daily for 4 days	No significant difference (no power stated)	D
Kaczmarzyk et al., 2007	Clindamycin pre-operatively only or clindamycin pre –operatively and post-operatively orally	No significant difference (no power stated)	D
Halpern et al., 2007	Penicillin i.v.	No cases of AO in both intervention and placebo group	I
Antiseptics			
Hermesch et al., 1998	Chlorhexidine mouth rinse pre-operative for 7 days and post-operative for 7 days	Significant difference (p-0.031)	A
Delilbasi et al., 2002	Chlorhexidine mouth rinse pre-operatively and post-operatively	No significant difference with chlorhexidine alone (no power stated)	D
Torres-Lagares et al., 2005	Chlorhexidine bio-adhesive gel	Significant difference (p=0.019)	A
Ragno et al., 1991	0.12% chlorhexidine mouth rinse on day of surgery and 7 days post-operative	Significant difference (p=0.008)	A

CTFR - Canadian Task Force Recommendations

A - good evidence to recommend the clinical preventive action.

B - fair evidence to recommend the clinical preventive action.

C - existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making.

D - is fair evidence to recommend against the clinical preventive action.

E - good evidence to recommend against the clinical preventive action.

I - insufficient evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

remaining two studies[28,30] did not report the power of the study.

Antiseptics (Chlorhexidine)

The four studies analyzing the efficacy of chlorhexidine reported more congruent results. Two studies comparing chlorhexidine rinses to placebo rinses[32,33] (p=0.031 and p=0.008 respectively) and one study comparing chlorhexidine bio-adhesive gel to placebo gel[34] (p=0.019) demonstrated statistically significant reductions in the incidence of post-operative AO. Another study comparing chlorhexidine alone versus chlorhexidine with amoxicillin plus clavulanic acid, using a saline placebo, found no statistically significant reduction in the chlorhexidine only group, although the power was not reported in this study[35]. However, significance was achieved when chlorhexidine was administered with amoxicillin plus clavulanic acid.

Discussion

The objective of this study was to review current and past literature to identify the most efficacious preventive measure of AO in third molar extractions. Antifibrinolytics, steroids, and clot-supporting agents were not included, since no rigorous studies on these preventive strategies were found. Conversely, a number of high-quality papers exploring the use of antibiotics and antiseptics were available, including several review papers that have been published in the last decade.

No conclusions could be drawn from this systematic review regarding antibiotic use in preventing AO due to the various methodologies used in administering the drugs in the selected studies. Only one study was rated as high quality, while the remaining five papers had only a fair level of evidence or inconclusive evidence. The major issue common between the papers was a lack of statement on power when there was no significant difference found. The absence of standardized surgical approaches within the studies also limited the quality of these papers. However, it is interesting to note that Akota *et al.* produced significant positive results with the local application of antibiotics, which may be advantageous since the antibiotics are applied directly to the extraction site, thereby bypassing the risk of systemic adverse effects. Other published studies on the local application of medicated gauze also reported positive results[37].

Two meta-analyses in the literature also investigated the efficacy of prophylactic antibiotic use. Hedstrom *et al.* reviewed 8 RCTs in 2007, and determined that tetracycline was the most effective antibiotic, while penicillin, amoxcillin and clindamycin yielded inconsistent results[19]. The authors found that the number-needed-to-treat (NNT) for the tetracycline studies were all positive and ranged from 3 to 8[19]. Ren and Malmstrom also conducted a meta-analysis in 2007 on antibiotics and found an overall NNT of 13 based on 2932 patients in 16 different clinical trials[20]. They concluded that both broad- and narrow-spectrum antibiotics were effective, which generally agrees with other available systematic reviews[2,12,21].

The results from the antibiotic studies in this review do not agree with other literature reviews, indicating that further research is needed. This is imperative, since there are increasing concerns with prescribing antibiotics due to possible allergic reactions and development of antibiotic resistance[12]. The American Dental Association also recognizes these risks based on the available evidence, and has recently altered their guidelines in prescribing antibiotics to high-risk patients[38]. Since AO is a self-limiting condition, the risks may outweigh the benefits if antibiotics are unnecessarily and irresponsibly administered.

The second extensively studied preventive method is the use of antiseptics – in particular chlorhexidine rinses. All four studies in this review have relatively large sample sizes with good RCT protocols, producing higher strengths of evidence. Only one of the three studies yielded no significant results; however, no power study was provided by the authors[35].

A meta-analysis published by Caso *et al.* in 2005 reported that multiple rinses of chlorhexidine significantly reduced the incidence of AO (relative risk = 1.90, CI 1.46, 2.47, p=0.05), whereas single rinses immediately before surgery were ineffective[8]. The evidence from this review also suggests that pre- and post-operative daily rinses with chlorhexidine are effective in preventing AO, which is consistent with other systematic reviews[2,12,21,32-34]. In addition, the possible side effects of chlorhexidine are minor and include staining of teeth, alterations in taste, and bad taste[35].

There are, however, several inherent limitations in this paper. Firstly, the incidence of AO is most prevalent between 30 to 45 years old whereas most of the available literature had a large proportion of subjects between 18 and 30 years old[24,39,40]. This could be attributed to the fact that it is much easier to design a study based on an elective procedure such as wisdom teeth extraction. It has also been demonstrated that the incidence of AO is lower in the extraction of teeth other than third molars[23,41,42]. These factors may lead to study result bias, reduced generalizability, and may explain the wide range of incidences reported by the various studies.

Another factor affecting incidence rates is the variability in the experience of the surgeon and the type of surgery performed, since the incidence of AO has been shown to increase with decreased operator experience[43]. In addition, the large range in the incidence of AO makes it difficult to calculate the sample size needed to provide a sufficient power. This may explain why none of the reviewed papers calculated the sample size pre-emptively. Ren *et al*. stated in a review that in order to reduce the incidence rate from 15% to 5%, a sample size of 318 subjects are required to achieve a power of 80%[20]. According to this calculation, none of the studies in this review obtained an adequate sample size.

Furthermore, only English literature was searched, limiting this review to the prevention and management techniques of English-speaking populations only. It is also unknown at this point whether AO prevalence may vary between racial/ethnic backgrounds.

Nonetheless, strengths of this literature review included the strict inclusive and exclusive criteria; in particular, the exclusion of high risk patients and the inclusion of specific diagnostic criteria. Older studies had a tendency to employ weak diagnostic criteria due to the inconsistent definition of AO in the past[2]. Various search methodologies, including searches of available thesis papers, grey literature, and expert opinions on the topic, were also utilized to reduce publication bias.

Conclusion

Based on this literature review, it can be concluded that there is insufficient evidence to recommend the administration of antibiotics to prevent AO. The local application of antibiotics may possibly become a preferred method of prevention for moderate-risk patients in the future, but more studies, as well as investigations of possible side effects, are required. Conversely, this literature review recommends the use of the antiseptic chlorhexidine for the prevention of AO if the surgeon wishes to take extra precaution. Since chlorhexidine is associated with minimal side effects, it is highly suggested for patients with increased risk, such as smokers, individuals with poor oral hygiene, and women on oral contraceptives.

Additional research is needed in all aspects of AO prevention. It is recommended that researchers investigating this topic should 1) standardize the type of surgical approach and account for surgeon experience; 2) utilize stringent inclusion and exclusion criteria; 3) calculate the sample size before initiating the study and provide a power analysis; 4) conduct studies that compare various antibiotics and different routes of administration (e.g. oral versus topical); and 5) compare different preventive measures, such as antibiotics versus antiseptics, within the same study. Ideally, a specific guideline on the prophylactic

management of AO during dental extractions should be developed from the available scientific evidence to benefit general practitioners and oral surgeons in providing optimal patient care.

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References

1. Crawford JY. Dry Socket. Dent Cosmos. 1896;38:929.

2. Blum IR. Contemporary views on dry socket (alveolar osteitis): a clinical appraisal of standardization, aetiopathogenesis and management: a critical review. Int. J. Oral Maxillofac. Surg. 2002; 31:309-317.

3. Fazakerley M, Field EA. Dry socket: A painful post-extraction complication (a review). Dent Update 1991;18:31-4.

4. Colby RC. The general practitioner's perspective of the etiology, prevention, and treatment of dry socket. Gen Dent 1997;461-7.

5. Report of a workshop on the management of patients with third molar teeth. J Oral Maxillofac Surg 1994;52:1102-12.

6. Al-Khateeb TL, el-Marsafi AI, Butler NP. The relationship between the indications for the surgical removal of impacted third molars and the incidence of alveolar osteitis. J Oral Maxillofac Surg. 1991 Feb;49(2):141-5.

7. Alling CC III, Helfrick JF, Alling RD. Impacted teeth. Philadelphia: Saunders; 1993, p.371.

8. Caso A, Hung LK, Beirne OR. Prevention of Alveolar Osteitis with Chlorhexidine: A meta-analytic review. Feb 2005; 99:155-9.

9. Larsen PE. Alveolar osteitis after surgical removal of impacted mandibular third molars. Identification of patients at risk. Oral Surg Oral Med Oral Pathol 1992; 73: 393-397.

10. Lilly GE, Osbon DB, Rael EM, Samuels HS, Jones JC. Alveolar osteitis associated with mandibular third molar extractions. J AM Dent Assoc 1974;88(4):802-6.

11. Sisk AL, Hammer WB Shelton DW, Joy ED Jr. Complications following removal of impacted third molars: the role of the experience of the surgeon. J Oral Maxillofac Surg 1997; 44(11):855-9.

12. Noroozi AR, Philbert RF. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics. 2009;107:30-35.

13. Houston JP, McCollum J, Pietz D, Schneck D. Alveolar osteitis: a review of its etiology, prevention, and treatment modalities. Gen Dent 2002;50:457-63.

14. Brin H. Etiology and pathogenesis in fibrinolytic alveolitis (dry socket). Int J Oral Surg. 1973;2:211-63.

15. Birn, H. Antifibrinolytic effect of Apernyl in "dry socket". Int J Oral Surg. 1972;1(4):190-4.

16. Awang MN. The aetiology of dry socket: a review. Int Dent J. 1989 Dec;39(4):236-40.

17. Birn, H. Fibrinolytic activity of alveolar bone in "dry socket". Acta Odontol Scand. 1972 Mar;30(1):23-32.

18. Nitzan DW. On the genesis of "dry socket". J Oral Maxillofac Surg. 1983 Nov;41(11):706-10.

19. Hedström L, Sjögren P. Effect estimates and methodological quality of randomized controlled trials about prevention of alveolar osteitis following tooth extraction: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Jan;103(1):8-15.

20. Ren YF, Malmstrom HS. Effectiveness of Antibiotics Prophylaxis Third Molar Surgery: A Meta-Analysis of Randomized Controlled Clinical Trials. American Association of Oral and Maxillofacial Surgeons. 2007; 65: 1909-921.

21. Vezeau PJ. Dental Extraction Wound Management: Medicating Postextraction Sockets. J. Oral Maxillofac. Surg. 2000;58: 532-537.

22. Gregg, TA. National Clinical Guidelines 1997. The Faculty of Dentistry of the Royal College of Surgeons of England. 1997.

23. Heasman PA, Jacobs DJ. A Clinical Investigation into the Incidence of Dry Socket. British Journal of Oral and Maxillofacial Surgery. 1984; 22: 115-122.

24. Ogunlewe MO, Adeyemo WL, Ladeinde AL, Taiwo OA. Incidence and pattern of presentation of AO following non-surgical tooth extraction. Nig Q J Hosp Med. 2007 Oct-Dec;17(4):126-30.

25. Fletcher RH, Fletcher SW, Wagner EH. (1996). *Clinical epidemiology – the essentials* (3rd ed.). Philadelphia: Williams & Wilkins.

26. Canadian Task Force on Preventive Health Care. (1997). *CTFPHC History/Methodology*. Retrieved January 8, 2008 from http://www.ctfphc.org/ctfphc&methods.htm#mid

27. Akota I, Alvsaker B, Bjornland T. The effect of locally applied gauze drain impregnated with chlortetracycline ointment in mandibular third-molar surgery. Acta Odontologica scandinavica. 1998; 56(1): 25-29.

28. Curran JB, Kennett S, Young AR. An assessment of the use of prophylactic antibiotics in third molar surgery. Int. J. Oral Surg. 1974; 3: 1-6.

29. Halpern LR, Dodson TB. Does prophylactic administration of systemic antibiotics prevent postoperative inflammatory complications after third molar surgery? J. Oral Maxillofac. Surg. 2007; 65: 177-185.

30. Kaczmarzyk T, Wichlinshi J, Stypulkowska J, Zaleska M, Panas M, Woron J. Single-dose and multi-dose clindamycin therapy fails to demonstrate efficacy in preventing infectious and inflammatory complications in third molar surgery. Int. J. Oral Maxillofac. Surg. 2007; 36: 417-422.

31. Ritzau M, Hillerup S, Branebjerg PE, Ersbol BK. Does metronidazole prevent alveolitis sicca dolorsa? A double-blind, placebo-controlled clinical study. Int. J. Oral Maxillofac. Surg. 1992; 21: 299-302.

32. Hermesch CB, Hilton TJ, Biesbrock AR, Baker RA, Cain-Hamlin J, McClanahan SF, Gerlach RW. Perioperative use of 0.12% chlorhexidine gluconate for the prevention of alveolar osteitis. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics. 1998;85:381-7.

33. Ragno JR, Szkutnik AJ. Evaluation of 0.12% chlorhexidine rinse on the prevention of alveolar osteitis. Oral Surg Oral Med Oral Pathol. 1991;72:524-6.

34. Torres-Lagares D, Gutierrez-Perez JL, Infante-Cossio P, Garcia-Calderon M, Romero-Ruis MM, Serrera-Figallo MA. Randomized, double-blind study on effectiveness of intra-alveolar chlorhexidine gel in reducing the incidence of alveolar osteitis in mandibular third molar surgery. Int. J. Oral Maxillofac. Surg. 2006;35:348-351.

35. Delilbasi C, Saracoglu U, Keskin A. Effects of 0.2% chlorhexidine gluconate and amoxicillin plus clavulanic acid on the prevention of alveolar osteitis following mandibular third molar extractions. Oral Surg Oral Med oral Pathol Radiol Endod 2002; 94: 301-4.

36. Bloomer CR. Alveolar osteitis prevention by immediate placement of medicated packing. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics. Sept 2000;90(3):282-284.

37. Pankhurst CL, Lewis DA, Clark DT. Prophylactic application of an intra-alveolar socket medicament to reduce postextraction complications in HIV-seropositive patients. Oral Surg Oral Med Oral Pathol. 1994 Apr;77(4):331-4.

38. Wilson et al. An updated legal perspective on antibiotic prophylaxis: American Dental Association Division of Legal Affairs. J Am Dent Assoc 2008;139;10S.

39. MacGregor AJ. Aetiology of dry socket: a clinical investigation. Br J Oral Surg 1968;6:49-58.

40. Rood JP, Murgatroyd J. Metronidazole in the prevention of 'dry socket'. Br J Oral Surg. 1979 Jul;17(1):62-70.

41. Nusair YM, Younis MH. Prevalence, clinical picture, and risk factors of dry socket in a Jordanian dental teaching center. J Contemp Dent Pract. 2007 Mar 1;8(3):53-63.

42. Singh AS, Mohamed A, Bouckaert MM. A clinical evaluation of dry sockets at the Medunsa Oral Health Centre. SADJ. 2008 Oct;63(9):490, 492-3.

43. Larsen, PE. The Effect of Chlorhexidine rinse on the Incidence of Alveolar Osteitis following the Surgical Removal of Impacted Mandibular Third Molars. J Oral Maxiloofac Surg. 1991;49:932-937.

APPENDIX

APPENDIX

Table 5: Evidence based table for Antibiotics

Author, date	Population	Intervention (number treated)	Control (number treated)	Outcome	Results	Critical Appraisal
Akota et al., 1988 Olso, Norway	**n**=26 patients, bilaterally impacted mandibular third molars **Age**: 20-37 (mean 25), 17 women, 9 men **Setting**: University of Oslo	3x1 cm gauze drain impregnated with chlortetracycline ointment inserted into socket for 3 days post-operatively (not stated)	No-drain treatment (not stated)	**Method of measurement:** Patients were seen in 3rd and 7th day after surgery and observed independently by 2 persons other than surgeon. **Postoperative alveolitis**: Defined by disintegeration of blood clot, exposure of alveolar bone, increased pain in alveolus region and/or irradiating pain after an intermediate period of no or low-intensity pain, foul odour, and exudate and/or pus in the socket. Overall incidence of 19%. **Pain and swelling**: registered on a 100-mm visual analogue scale at 3, 7, 11 hours post-operatively and continued twice daily at 0900 h and 2100 h until the 6th postoperative day. **Mouth Opening**: measured pre-operatively, and on the 3rd and 7th day post-operatively, by 2 independent observers with a ruler as the distance between the edges of the upper and lower central incisors; the highest measurement was recorded.	**Postoperative alveolitis**: 4% in drain group and 35% in no-drain group. Statistically significant (P=0.02) **Pain**: No statistically significant difference (P=0.04) **Swelling**: No statistically significant difference except in morning (P=0.04) and evening (P=0.01) of the 1st postoperative day with less swelling in the no-drain group. **Mouth Opening**: No statistically significant difference.	**Checklist score:** 12/17 **Major strengths:** Randomized split mouth design; appropriate inclusion/exclusions; VAS for pain **Major weaknesses:** **No calculation of sample size before study, n**o blinding; inability to distinguish if effect was due to chlortetracycline or the act of drainage **Strength of evidence:** **B**-I
Ritzau et al., 1992 Copenhagen, Denmark	**n**= 270 patients, impacted (partially or totally) mandibular third molar **Age**= 25 (median), SD=4.8, 56% being 20-24, 133 female, 137 male **Setting**: Royal Dental Collegs of Copenhagen and Arhus	Single dose of 2 tablets with a total dose of 1000 mg metronidazole 30 minutes pre-operatively (135 patients, 63 female, 72 male)	Placebo (135 patients, 70 female, 65 male)	**Method of measurement:** Follow-up examination scheduled 1 week after surgery and patients were urged to report to the clinic in case of any complication **Alveolitis sicca dolorosa (ASD):** defined as 1) severe pain irradiating from the empty socket towards the (ipsilateral) ear, and 2) disintegration (partial or total) of the socket coagulum. Overall incidence of 4.8%.	**Alveolitis sicca dolorosa (ASD):** No difference between treated group (4.4%) and placebo group (5.2%), (2 tailed P value = 1.00), nor males (8) and females (5), (P=0.407)	**Checklist score:** 9/17 **Major strengths:** Blinding **Major weaknesses:** **No calculation of sample size before study** ,low power study (5%); no VAS, surgeries were performed by different surgeons **Strength of evidence:** I-I

Author, date	Population	Intervention (number treated)	Control (number treated)	Outcome	Results	Critical Appraisal
Delilbasi et al., 2002 Ankara, Turkey	**n**= 177 patients, impacted mandibular third molar **Age**: mean 24, 82 male, 95 female **Demographics**: women using contraceptives excluded **Setting**: Not stated	Group 1: Chlorhexidine rinse pre-operative and twice daily post-operatively for 7 days (62) Group 2: Chlorhexidine rinse pre-operative and twice daily post-operatively for 7 days , AND amoxicillin plus clavulanic acid combination twice daily for 5 days (n=56)	Sterile saline solution rinse pre-operatively and post-operatively (n=59)	**Method of measurement:** Post-operative examinations where performed on the 3rd and 7th days to determine any adverse reactions and assess the presence of alveolar osteitis. **Alveolar osteitis:** Diagnostic criteria by Bloomer. If the patient reported pain unrelieved by analgesics and if exposed bone or necrotic debris was present, the diagnosis of alveolar osteitis was made clinically. Overall incidence of 18%.	**Sutures:** No statistical difference (P=0.823, ANOVA) **Operation Time**: No statistical difference (P=0.615, ANOVA) **Alveolar osteitis**: 20.9% in chlorhexidine only group, 8.9% in the chlorhexidine and amoxicillin-plus-clavulanic acid group, 23.7% in saline-only group. Statistically significant reduction in the anti-biotic group (P=0.001, x^2) **Complaints**: chlorhexidine causing staining of dentures and oral mucosa, alteration in taste and bad taste of solution.	**Checklist score:** 10/17 **Major strengths:** Blinding; noted adverse effects of CHX **Major weaknesses:** **No calculation of sample size before study** , no VAS; surgeries performed by different surgeons; no studies of adverse effects of amoxicillin plus clavulanic acid, no power stated **Strength of evidence:** B-I
Curran et al., 1974 Winnipeg, Manitoba, Canada	**n**= 68 patients, 133 bone impacted mandibular third molars **Age**: mean 22.2, 28 male, 40 female **Setting**: Not stated	Penicillin G 1 million iu intramuscular injection 1 hour pre-operatively followed by 250 mg penicillin orally 4 times daily for 4 days, but if allergy to penicillin then patient received erythromycin (not stated)	No antibiotics (not stated)	**Method of measurement:** Observations on all patients were made by one clinician without knowledge of which group the patients had been assigned to. On the 1st, 4th, and 7th post-operative days, the following parameters were measured: **Trismus**: Defined as being present when incisal opening was less than 75% of the patient's normal opening. Incisal opening was graded as 0=absent, 1=just visible and palpable, 2=obvious, and 3=severe. **Swelling:** Graded as 0=absent, 1=just visible and palpable, 2=obvious, and 3=severe. **Pain**: Pain was estimated by giving all patients a uniform number of an analgesic and asking them to record daily the presence of pain and the number of analgesic tablets required to control it. **Infection (AO)**: expressed as "dry socket", which was diagnosed, in descending order of importance, as 1) severe persistent neuralgic pain, not controlled fully by the analgesic	**Trismus**: Day 1 – 90.9%, day 4 – 72.7% and day 7 – 42.4% in antibiotics group. Day 1 – 91.4%, day 4 – 60% and day 7 – 51.4% in antibiotics group. **Swelling**: Slight differences between groups; not statistically significant **Pain**: Absent from 56 patients on 7th day, if present after then directly related to dry socket. **Infection (AO)**: 15% of patients and 7.8% of sockets in antibiotics group, 14.3% of patients and 8.7% of sockets in control group. Only 1 of 9 control group and 1 of 13 antibiotics group with history of pericoronitis infected. No statistically significant difference. **Difficulty of surgery:** Infection more likely if extraction difficult. 3 infected of 32 difficult in antibiotics group, 6 infected of 45 difficult in control group. Sample too	**Checklist score:** 9/17 **Major strengths:** Double blinding **Major weaknesses:** **No calculation of sample size before study**; weak inclusion/exclusion criteria; different antibiotics used; no VAS; surgeries performed by different surgeons; no calculation of power **Strength of evidence:** D-I

Author, date	Population	Intervention (number treated)	Control (number treated)	Outcome	Results	Critical Appraisal
				provided, and relieved by socket irrigation and insertion of a dressing, 2) clot disintegeration with denuded alveolar bone, and 3) putrid odour. **Difficulty of surgery:** assessed by recording tooth position, amount of bone removal, need for tooth dissection, and time taken from incision to closure at each operative site	small for statistical significance.	
Kaczmarzyk et al., 2007 Krakow, Poland	**n**= 86 patients, lower third molar requiring bone removal **Age**: mean 23.8, 63 female, 23 male **Setting**: Jagiellonian University	Group 1: Single dose of oral clindamycin 600 mg 60 minutes preoperative, followed by 300 mg placebo every 8 hours for 5 days (31) Group 2: Single dose of oral clindamycin 600 mg 60 minutes preoperative, followed by 300 mg clindamycin every 8 hours for 5 days (28)	Placebo (27)	**Method of measurement:** On the 1st, 2nd, and 7th post-operative days, patients were evaluated for trismus, facial swelling, and lymphadenopathy on a three-grade scale; body temperature was taken each time the patient self-reported pain; and subjective pain sensation was graded by a 100-mm visual analogue scale. Alveolar osteitis was diagnosed under the presence of a necrotic grey clot in a bare bony socket, accompanied by pain.	**Postoperative alveolar osteitis**: 3.23% in single dose group, 7.14% in 5-day group, 14.81% in placebo group, no statistically significant difference between any of the 3 groups (P=0.26, x^2). Tooth location and alveolar osteitis not statistically significant (P=0.6, x^2) **Pain**: Not statistically significant (P=0.46 [day1], 0.86 [day2], 0.37 [day7], Kruskal-Wallis rank test). Tooth location and pain not statistically significant. **Body Temperature**: Not statistically significant on days 1 (P=0.59), and 2 (P=0.78), but day 7 significant (P=0.03) (Kruskal-Wallis rank test) **Trismus**: Not statistically significant days 1 (P=0.28,x^2), 7 (P=0.64,x^2), and barely significant day 2 (P=0.05537, x^2) **Facial Swelling**: No statistically significant difference.	**Checklist score:** 12/17 **Major strengths:** Double blinding; good inclusion/exclusion criteria; VAS; adverse events to clindamycin noted **Major weaknesses:** **No calculation of sample size before study**; no statement of power **Strength of evidence:** D-I
Halpern et al., 2007 Boston, Massachusetts, USA	**n**=118 patients, impacted third molar, averaged 3.5 M3s extracted each **Age**: mean 25.4 (SD 7.2), 61 females, 57	Intravenous penicillin or if allergic then clindamycin placed into the alveolus (59)	Placebo, saline (59)	**Method of measurement:** Outcomes were assessed at the subject level via follow-up visits scheduled 7 days post-operatively by the operating surgeon or appointed representative through a physical examination that focused on 2	**Surgical site infection (SSI)**:0% of treatment group, 8.5% of placebo group **Alveolar osteitis (AO)**: 0% of treatment group, 0% of placebo group	**Checklist score:** 11/17 **Major strengths:** Good inclusion/exclusion criteria; double blinding; analysis of demographic and

Author, date	Population	Intervention (number treated)	Control (number treated)	Outcome	Results	Critical Appraisal
	males **Demographics**: 79% white, 75% never smoked, 48% no medication, 32% no alcohol **Setting**: Massachusetts General Hospital			relevant complications: **Surgical site infection (SSI)**: Diagnosis of SSI was made if there was visual evidence of purulence in one or more of the extraction sites and a Gram's stain showing the presence of white blood cells. **Alveolar osteitis (AO)**: Diagnosis of AO was made if all of the following were present: 1) there was a new onset or increasing pain more than 36 hours post-operative, 2) there was a loss of blood clot in the extraction site evidence by exposed bone, 3) gentle probing or irrigation of the would duplicated the pain, and 4) there was significant pain relief after application of an anodyne dressing.		medical history variables between study groups **Major weaknesses:** **No calculation of sample size before study** ; no study of adverse outcomes of antibiotics; no statement of power; surgeries performed by different surgeons **Strength of evidence:** I-I

Table 6: Evidence based table for Antiseptics

Author, date	Population	Intervention (number treated)	Control (number treated)	Results	Outcome	Critical Appraisal
Hermesch et al., 1998 San Antonio, Teaxas, USA	**n**= 271 patients, 503 impacted mandibular third molar, military personnel and families **Age**: 18-52 (mean 22), 170 female, 101 male **Demographics**: 35% of females on oral contraceptives, 15.6% of patients current smokers **Setting**: Military dental clinic	0.12% Chlorhexidine mouthrinse 30 seconds twice a day for 7 days pre-operative and 7 days post-operative for 15 consecutive days (136)	Placebo mouthrinse with same instructions (135)	**Method of measurement:** After surgery, any subjects reporting symptoms was seen immediately for clinical evaluation. Subjects were contacted by telephone 3-4 days pos-operatively to evaluate post-operative status; on the 7th day after surgery each subject received a routine pos-operative evaluation for presence of alveolar osteitis by two attending clinical examiners involved in the study, without knowledge of treatment assignment. **Alveolar osteitis**: Diagnosed on the basis of collaborative clinical and subjective findings. Clinical findings include evidence of one or more of the following: loss of blood clot, necrosis of blood clot, and exposed alveolar bone. Subjective findings include reports of	**Alveolar osteitis**: 18.4% in chlorhexidine group, 29.6% in placebo group. Statistically significant (P=0.031, OR=1.87). Extraction based incidence: 13% in chlorhexidine group, 23.3% in placebo group (P=0.014, OR=2.05). Incidence of alveolar osteitis 38.9% in females using oral contraceptives, 20.7% in females not using oral contraceptives (P=0.035, OR=1.92). Smoking not statistically significant (P=0.33, OR=1.20) **Safety**: Safe. 16.2% of chlorhexidine group experienced total 30 adverse events. 23.0% of placebo	**Checklist score:** 10/17 **Major strengths:** Blinding; adverse effects of treatment were analyzed **Major weaknesses:** **No calculation of sample size before study;** no VAS; rinsing was performed unsupervised at home; surgeries performed by different surgeons **Strength of evidence:** A-I

Author, date	Population	Intervention (number treated)	Control (number treated)	Results	Outcome	Critical Appraisal
				persistent or increasing post-operative pain after surgery, with throbbing pain at the surgical site that was not relieved with mild analgesics.	group experienced total 49 adverse events.	
Torres-Lagares et al., 2005 Seville, Spain	**n**= 103 patients, 103 impacted third molars **Age**: 18-60 (mean 26), 69 female, 34 male **Demographics**: 26 smokers, 10 women on oral contraceptives – each split evenly between groups **Setting**: University of Seville	Bio-adhesive gel to deliver CHX more directly and prolonged (53)	Placebo gel (50)	**Method of measurement:** Diagnosis of post-operative alveolar osteitis was made based on the diagnostic criteria standardized by Blum.	**Postextraction alveolar osteitis (AO):** 11% in treatment group, 30% in placebo group, statistically significant (P=0.019, x^2).	**Checklist score:** 13/17 **Major strengths:** Analyzed the significance of differences in demographics, difficulty of extraction, and tolerance to treatment between groups; double blinding **Major weaknesses:** **No calculation of sample size before study;** No statement of surgical methods used **Strength of evidence:** A-I
Ragno et al., 1991 Washington, DC, USA	**n**= 80 patients, 160 third molar extractions **Age**: 18+ **Demographics**: 1 woman who smoke and not taking oral contraceptives, 15 women who do not smoke and taking oral contraceptives, 13 women not taking oral contraceptives, 16 men who smoke, 35 men who do not smoke **Setting**: Army medical center	0.12% chlorhexidine solution rinse 15 ml for 30 second immediately before surgery and twice a day for 7 days post-operatively (40)	Placebo with same instructions (40)	**Method of measurement:** Post-operative examination was performed on the 3rd and 7th days to determine an adverse reactions and the presence of alveolar osteitis. **Alveolar osteitis (AO):** Diagnosed by the presence of a necrotic blood clot or absence of a blood clot; foul odour; increase in the postoperative pain unrelieved by analgesics; and the absence of clinical signs of gross infection.	**Alveolar osteitis (AO):**17.5% of sockets and 25% of patients in treatment group, 36% of sockets and 50% of patients in placebo group, statistically significant (P=0.008, Yates corrected x^2)	**Checklist score:** 12/17 **Major strengths:** Double blinding, stratification of patients into risk groups and analysis of results between risk groups, analysis of adverse outcomes to CHX **Major weaknesses:** **No calculation of sample size before study;** no VAS used, unmonitored post-surgical rinsing at home **Strength of evidence:** A-I
Delilbasi et al., 2002	**n**= 177 patients, impacted	Group 1: Chlorhexidine rinse	Sterile saline solution rinse pre-	**Method of measurement:** Post-operative examinations where	**Sutures:** No statistical difference (P=0.823, ANOVA)	**Checklist score:** 10/17

Author, date	Population	Intervention (number treated)	Control (number treated)	Results	Outcome	Critical Appraisal
Ankara, Turkey	mandibular third molar **Age**: mean 24, 82 male, 95 female **Demographics**: women using contraceptives excluded **Setting**: Not stated	pre-operative and twice daily post-operatively for 7 days (62) Group 2: Chlorhexidine rinse pre-operative and twice daily post-operatively for 7 days , AND amoxicillin plus clavulanic acid combination twice daily for 5 days (n=56)	operatively and post-operatively (n=59)	performed on the 3rd and 7th days to determine any adverse reactions and assess the presence of alveolar osteitis. **Alveolar osteitis:** Diagnostic criteria by Bloomer. If the patient reported pain unrelieved by analgesics and if exposed bone or necrotic debris was present, the diagnosis of alveolar osteitis was made clinically. Overall incidence of 18%.	**Operation Time**: No statistical difference (P=0.615, ANOVA) **Alveolar osteitis**: 20.9% in chlorhexidine only group, 8.9% in the chlorhexidine and amoxicillin-plus-clavulanic acid group, 23.7% in saline-only group. Statistically significant reduction in the anti-biotic group (P=0.001, x^2) **Complaints**: chlorhexidine causing staining of dentures and oral mucosa, alteration in taste and bad taste of solution.	**Major strengths:** Blinding; noted adverse effects of CHX **Major weaknesses:** **No calculation of sample size before study;** no VAS; surgeries performed by different surgeons; no studies of adverse effects of amoxicillin plus clavulanic acid, no power stated **Strength of evidence:** B-I

Table 7: List of articles excluded and reason for exclusion

Article	Reason for exclusion
Lagares et al., 2005	Study was a pilot study
Hooley et al., 1995	Authors based diagnosis of alveolar osteitis on patient report of pain
Hita-Iglesias et al., 2008	Control group consisted of a different method of treatment application. No placebo or no treatment group was used as a control.
Johnson et al., 1998	No age range of participants stated and no randomization stated
Mentin et al., 2006	Study was a comparison of two different application techniques of the same treatment. No placebo or no treatment group was used as a control. Age range did not fit our inclusion criteria
Lilly et al., 1974	Did not exclude any systemic diseases and age range did not fit our inclusion criteria
Monaco et al., 1999	Did not exclude any systemic diseases and age range did not fit our inclusion criteria
Poeschl et al., 2004	Did not exclude any systemic diseases and age range did not fit our inclusion criteria
Kupfer, 1995	Study was a retrospective study
Fotos et al., 1992	No specific exclusion criteria were mentioned except current infection at surgical site
Swanson et al., 1989	Groups not similar at beginning of trial.
Sweet et al., 1985	Not all clinically important outcomes were considered.
Sanchis et al., 2004	No randomization of patients to groups (retrospective case control study).
Sorenson et al., 1987	Outcomes and interventions not validly and reliably measured, no blinding.
Poor et al., 2002	No randomization of patients to groups
Schatz et al., 1987	No control/placebo group
Sweet et al., 1976	Intervention utilized was not listed in inclusion criteria.
Rutledge et al., 1984	No mention of patient age and medical conditions. Small sample size.
Julius et al.,	No control group
Vedtofte et al.,	Study did not exclude extractions due to infection
Krekmanov et al., 2007	No randomization stated
Rood et al,	No randomization and did not limit to only third molar extractions
Cheung et al.,	Study was based on surgical prevention and did not limit to third molar extractions
Hyrkas et al,	No exclusion criteria stated
Bergdahl et al., 2004	Included patient with extractions due to infection
Berwick et al., 1990	Study was a pilot study
Bloomer et al., 2000	Control group was not placebo or no intervention, and no randomization stated
Bonine, 1995	No randomization stated
Butler, 1977	No control group
Bystedt et al., 1980	Focused on post-operative complications but did not do in-depth analysis on AO
Chapnick, 1992	No control group and no exclusion criteria