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Aetiology, Prevention and Management of Alveolar Osteitis – A Scoping Review

Short title: Alveolar osteitis – aetiology, prevention, management

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Abstract

Background. Alveolar osteitis (AO) is a poorly understood, common, painful complication following exodontia. It is sometimes managed by inappropriate prescription of antibiotics which contributes to the global threat of antimicrobial resistance. Use of intra-alveolar chlorhexidine also presents a serious risk of anaphylaxis to the patient.

Objective. This scoping review aims to investigate the aetiology, prevention and management of AO and highlight the extent of inappropriate prescribing and intra-alveolar chlorhexidine use.

Design. A scoping review was undertaken using the PRISMA guidelines. Medline, Ovid and Pubmed were searched between 2010 and 2020, from which 63 studies were selected for review that related to the aetiology, prevention or management of AO. Data was analysed for frequency of studies reporting information on risk factors for aetiology, prevention strategies and management including inappropriate management using antibiotic prescribing and intra-alveolar chlorhexidine.

Results. Impaired immune response, surgical technique, and age were identified as significant factors in the development of AO, whilst there is conflicting evidence regarding the effects of smoking and gender. With regards to prevention, the use of prophylactic antibiotics is not supported within the literature. Saline irrigation and eugenol pastes used preventively have been shown to be cheap and effective alternatives to chlorhexidine with no adverse effects. Hyaluronic acid and low-level laser therapies showed a significant reduction in pain and soft-tissue inflammation in the management of AO compared to Alveogyl.

Conclusions. Further understanding of the pathophysiology of AO is needed, in addition to large high-quality RCTs or long-term observational studies into the aetiology, prevention and management of AO to produce up-to-date evidence-based clinical guidelines.

Clinicians should also be mindful of their contribution to growing antimicrobial resistance and avoid inappropriate prescribing of antibiotics. Saline should replace chlorhexidine as the intra-alveolar irrigant of choice.

Keywords: Surgery, oral; Dentistry; Dry socket; Molar, third; Tooth extraction

Introduction

Alveolar osteitis (AO) is a complication that can arise following exodontia. Currently, there is no universal terminology for the condition. The condition of "dry socket" was first described in 1896 by Crawford[73]. Other common terms include fibrinolytic alveolitis, localised alveolar osteitis, localised osteomyelitis and necrotic socket. Birn[4] coined the term fibrinolytic alveolitis in the 1970's. The literature describes this as perhaps the most accurate terminology, relating to the widely accepted fibrinolytic theory[4].Despite this, it remains one of the less-frequently used terms in the literature. Most commonly, the condition is referred to as "dry socket" or "alveolar osteitis". Definitions vary according to publications, for the purposes of this scoping review, the definition of AO is "*an area of exposed bone, characterised by the absence of a fibrin clot in an extraction socket, either due to a failure in clot formation or loss of the clot post-formation, with patients usually presenting in moderate to severe pain".* The reported incidence of AO varies widely in the literature, but according to a Cochrane Review it is most commonly reported to be between 0.5 and 5% for routine extractions[1]. The same review reports the incidence of AO following mandibular wisdom tooth extraction to be >30%. However, Blum reports the incidence to vary between 1-45%[2].

Physiological mechanisms involved with AO have not been extensively examined and are likely to be complex. To date, Birns fibrinolytic theory[4] remains the most widely accepted explanation. Traumatic force during extraction has been proposed to induce osteoblast death, local ischaemia and subsequently a lack of adhesion of necrotic osteoblasts within the fibrin clot[3], which may

contribute to the higher incidence of mandibular third molar AO following surgical extractions seen within the literature. High plasmin levels around extraction sockets have been noted following tooth extraction[4], which play a role in fibrinolysis and up-regulation of local inflammation which may contribute to the lack of fibrin clot development in AO cases.

AO has a significant burden on patients, is often reported as extremely painful following exodontia and can result in repeated return visits to primary or secondary care for symptomatic relief and management. This has implications in both cost and time-efficiency to the clinician, as well as prolonged discomfort for the patient. This prolonged discomfort may also serve to enforce already negative perceptions and fears surrounding access to dental care.

Chlorhexidine is regularly used as an intra-alveolar irrigant as part of surgical protocols despite guidelines to avoid its use following reports of rare but fatal anaphylactic reactions as well as an increasing incidence of hypersensitivity reactions to chlorhexidine products[60]. In addition to this, management by inappropriate prescription of antibiotics is not advocated for a condition that is largely understood to be inflammatory not infective. The extent of inappropriate antibiotic use for AO remains unclear and an important area to investigate as continued use contributes to the global threat of antimicrobial resistance.

The aim of this scoping review is therefore to investigate the aetiology, prevention and management of AO by reviewing the current literature. Specific objectives include:

1. Identifying risk factors for AO
2. Identifying prevention strategies for AO that can reduce burden on patients and healthcare service
3. Investigate current management including the extent of prescribing of unnecessary antibiotics and inappropriate intra-alveolar chlorhexidine use.

Methodology

Our protocol was drafted in using the PROSPERO format and is available on request from the corresponding author. The review was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Scoping Reviews extension (Appendix 1).

Search methods for the identification of studies

A search was conducted using the online databases Medline, Ovid and PubMed. The following search terms were used: “Alveolar osteitis OR dry socket OR fibrinolytic alveolitis OR localised alveolar osteitis OR localised alveolar osteomyelitis OR necrotic socket AND aetiology OR causes OR prevention OR management OR treatment” (detailed search strategy is included in appendix 2). The references of included studies were also hand searched for eligible studies that were not obtained through database searching. Articles in non-English language or pertaining to non-human participants were excluded. Case reports, Case series, comments on or publications relating to, letters to editors, book chapters and reviews were excluded. The date was restricted to articles published between 2010 and March 2020 as the review was intended to investigate current practices relevant to AO. Randomised controlled trials, case-controlled trials and cohort studies were included. Studies involving participants of all ages and both sexes, who had undergone any type of dental extraction, and pertaining to the aetiology, prevention or management of AO were included.

Outcome measures

Outcomes included the aetiological factors, preventive measures or management techniques relating to AO. Secondary outcomes included number of papers using intra-alveolar chlorhexidine or prescription of pre-, peri-, post-operative antibiotics inappropriately.

Data collection and analysis

The titles and abstracts of the articles were assessed by a single reviewer to determine if the inclusion criteria were met. For articles where insufficient information was available within the titles and abstracts, the full text was obtained and reviewed. Uncertainty by the first reviewer regarding article inclusion was resolved by discussion with a second reviewer. All studies included then underwent a validity assessment prior to data extraction.

The search produced 223 results. 58 duplicates were identified. After screening the titles and abstracts to assess the inclusion criteria was met, the full texts of the included articles were reviewed, and full text articles not meeting the inclusion criteria were excluded (Figure 1). The articles were subsequently split into 3 groups: articles investigating the aetiology of AO, the prevention of AO, and those investigating the management of AO.

Data extraction and analysis

Separate databases were created for the aetiology, prevention, and management of AO. Data was extracted and added to the relevant database. This was checked by the second reviewer.

1. For the *aetiology* of AO, the following data was recorded if available: Proposed aetiology being examined, statistical outcome measures, outcome, sample size, number of male and female participants, mean age (±SD) or age range, additional important findings (S1).

2. For the p*revention* of AO, the following data was recorded if available: type of procedure being performed, inclusion/exclusion criteria, study limitations, proposed preventive technique, outcome of the study, incidence and duration of AO (S2).

3. For the *management* of AO, the following data was recorded if available: type of procedure being performed, inclusion/exclusion criteria, study limitations, proposed management technique, outcome of the study, incidence and duration of AO (S3).

Results

The initial search returned 223 articles. 58 duplicates were identified. Following screening using the inclusion/exclusion criteria, 63 papers were selected for inclusion. Of these, 19 related to the *aetiology* of AO, 36 related to the *prevention* of AO, and 8 to the *management.* (Figure 1)

Aetiology

Participant details - In total, the articles included 6,531 dental extractions. 15 articles reported the gender of the participants totalling 2,464 males and 3,207 females. The mean ages noted ranged between 16 to 47.6 years old[8,9].

Study design - 9 of the studies were randomised controlled trials. 4 comparative studies, 1 observational study, 1 case control and 2 clinical studies were also included. It was not possible to obtain the full text for a further 2 articles.

Aetiological factors (Figure 2) - proposed aetiologies were organised into 2 categories - physiological or clinical factors. 4 papers proposed physiological aetiologies. Levitin et al[6], assessed 38 risk factors, but only included those with statistical significance in their results. Cancer, serious illnesses, history of dental complications, sinus problems, hepatitis, mouth sores and allergies were found to be statistically significant in the development of AO. Isik et al[7], assessed acute infection as a risk factor for the development of AO but found no significant difference in AO incidence between acutely infected vs non acutely infected teeth. Adeyemo et al[8], compared patients >40years with

those <40 years and concluded that increasing age was not a significant factor in the development of AO. Eshghpour[66] compared menstruating to mid-cycle females undergoing dental extractions, as well as comparing those on the oral contraceptive pill (OCP) with those who were not. A significant increase in AO incidence was found in OCP takers, as well as mid-menstrual cycle.

The remaining 13 papers proposed clinical related aetiologies. Mohajerani et al[9] noted a significant reduction in the incidence of AO using the modified triangular flap design following impacted 3rd molar surgery when compared to an envelope flap. Koyuncu[69] noted an increase in AO with modified triangular flaps however the difference compared to envelope flaps was not significant. In a similar study by Elo et al[10] comparing envelope flap, modified triangular flap and two experimental flap designs no significant difference in AO incidence between envelope and modified triangular flaps were noted. Both experimental flap designs showed a significant reduction in AO incidence. Menziletoglu[67] compared buccal and lingual flaps however no cases of AO were noted. Goldsmith[68] conducted an RCT comparing pedicle and buccal flaps and found no significant difference in AO incidence, however a higher incidence of AO was noted in the buccal flap group.

Jerjes[69] found a significant decrease in AO when comparing consultant versus registrar extractions.

In a randomised controlled trial comparing intra-ligamentary anaesthesia with inferior alveolar nerve blocks, Kammerer et al[11] noted no significant difference in AO incidence.

2 papers compared traditional surgical burs and piezosurgery[12,13] and found no significant difference in the incidence of AO.

Hariharan[14] compared physics forceps and extraction forceps in orthodontic premolar extractions, however no cases of AO were noted in either group.

Assessing primary vs. secondary closure in impacted third molar removal, Danda et al[15] found no significant difference in AO incidence between the two groups. Aydintug et al[16]

assessed drainage vs. secondary closure and concluded drainage seems to reduce complications such as AO in surgical extractions. Bello [70] conducted an RCT comparing partial and total wound closure and concluded there was no significant difference in AO incidence.

Prevention

Participant details – The articles included 9,545 patients. 3 articles could not be obtained for review. 31/33 articles reported the gender, including 4,569 males and 4818 females. Of the papers that included an age range, these ranged from 6-72 years.

Study design – 24 of the studies were randomised controlled trials, 4 were comparative studies, 3 cohort studies and 2 cross-sectional studies.

Prevention (Figure 3) – A cross-sectional study by Alsaleh[17] assessed the impact of compliance with post-operative instructions on the development of alveolar osteitis and concluded there is no significant relationship between compliance with post-operative advice and the development of alveolar osteitis. In addition to this, no significant relationship between smoking and AO or gender and AO was noted.

5 papers assessed the impact of antibiotics on the development of AO. A randomised controlled trial by Oyri[18] investigated the use of an intra-alveolar oxytetracycline drain and concluded that this significantly reduces the incidence of AO development.

Reiland[19] compared the post-operative and peri-operative use of systemic antibiotics, concluding that antibiotic regimen does not significantly influence AO development, however found that increasing age, and female patients are significantly more likely to develop AO.

3 randomised controlled trials assessed the efficacy of antibiotics at reducing the risk of developing AO[20,21,22]. Gbotolorun[21] and Xue[22] concluded that antibiotics do not significantly reduce the incidence of development of AO. Lang[20] noted a significant reduction in AO development in the antibiotic group, however it was noted that 40 patients would need to be treated with antibiotics in order to prevent 1 case of AO.

14 papers were concerned with the use of chlorhexidine to prevent AO. 7 randomised controlled trials assessed the efficacy of 0.2% chlorhexidine bio-adhesive gel at reducing the incidence of AO[23,24,25,26,52,53,56]. 4 papers[23,52,53,56] noted a significant reduction in AO incidence with intra-alveolar placement of 0.2% chlorhexidine gel, while 3 found no significant difference in AO incidence[24,25,26]. Freudenthal[24] also concluded that mean surgery time and smoking did not significantly affect AO incidence. This is in agreement with Rubio-Palau[25] who found that smoking and the oral contraceptive pill do not affect incidence of AO but found that difficulty of extraction significantly increased AO incidence. One RCT[27] compared 0.2% chlorhexidine gel with eugenol paste and found that both significantly reduced the incidence of AO, however the eugenol paste was a more effective preventive method.

Rodriguez-Perez[28] compared 0.2% and 1% chlorhexidine gels and concluded that there was no significant difference in AO incidence between the two gel strengths.

A randomised controlled trial by Halabi[29] assessed the use of 0.12% chlorhexidine rinse to prevent AO and noted a significant reduction in AO incidence when 0.12% chlorhexidine was used as a rinse twice daily for 7 days. Cho[30] compared 0.2% chlorhexidine rinsing with irrigation and found a significant reduction in AO incidence when irrigating for 7 days compared to rinsing.

A comparative study[31] assessed the use of saline vs. 0.12% chlorhexidine rinse and found no significant difference in AO incidence between the two interventions. Jadhao[32] compared

saline, chlorhexidine and povodine iodine irrigation and noted a significant reduction in AO incidence with chlorhexidine rinsing.

One randomised controlled trial[51] compared the use of 0.2% chlorhexidine gel and 0.12% chlorhexidine rinse however no significant difference in AO incidence was noted.

5 randomised controlled trials assessed the use of platelet-rich fibrin (PRF) in the prevention of AO[33,34,35,36,37]. Of these, 2 noted a significant reduction in AO incidence with PRF[35,37] while 3 found no significant reduction[33,34,36].

A single RCT[55] compared the use of PRF alone with the use of PRF and chlorhexidine in the prevention of AO. This study concluded that PRF significantly reduced the incidence of AO compared to no intervention. It also found that PRF and chlorhexidine significantly reduced the incidence of AO when compared to no intervention or the use of PRF alone.

A randomised controlled trial by Alissa et al[38] assessed the use of platelet-rich protein on the healing of extraction sockets and noted a borderline statistically significant reduction in AO ($p = 0.06$) although it should be noted that the sample size was 23.

One comparative study and one cohort study assessed the use of a resorbable collagen membrane to prevent AO[57,39]. While the results of the studies were not statistically significant, both noted a reduction in AO incidence with these membranes.

One randomised controlled trial and two comparative studies assessed the use of water/saline in the prevention of AO[40,41,42]. The RCT and one comparative study noted a significant reduction in the incidence of AO with saline irrigation[40,41], while a comparative study by Tolstunov[42] found a 55.6% increase in AO when post-extraction saline irrigation

was carried out, concluding that initial bleeding post-extraction plays an important role in intra-alveolar clot formation and thus a reduction in the incidence of AO.

One randomised controlled trial[58] considered the effect of a topical gel containing amino acids and sodium hyaluronate in the prevention of AO but found no significant reduction in AO incidence.

Management

Participant details – The articles included 483 patients – 239 males and 244 females. 6 articles included mean ages, ranging from 31.2-37.72

Study design – 5 of the studies were randomised controlled trials, with one cohort study and two comparative studies also included.

Management (Figure 4) – Two studies noted mean onset as 2-3 days respectively[45,46]. One study noted the duration of the condition to be 1-9 days, with an average of 4.8 days duration[47].

One RCT assessed the use of hyaluronic acid and aminocaproic acid with either irrigation or curettage, compared to the use of Alvogyl[43]. It concluded that hyaluronic acid, with or without the use of aminocaproic acid is more effective at providing a reduction AO-related in pain and inflammation compared to Alvogyl. Another cohort study[47] considered the use of a hyaluronic acid impregnated wound obturator in the management of AO, with a 96% success rate considered to be statistically significant, noting on average 4 applications were required, taking a mean of 4.8 days for the visual analogue score (VAS) to drop <20mm.

A comparative study[48] compared the use of low-level laser therapy with Alvogyl, noting that on day 1 Alvogyl was the most effective intervention in terms of pain relief, however by day 3 the low level laser therapy was the most effective intervention in terms of pain management, as well as achieving the closest-to-zero VAS score. One RCT[49] compared the use of SaliCept, Alvogyl and low-level laser therapy in the management of AO, concluding that all 3 interventions significantly reduced pain compared to the control, with low level laser therapy the most effective intervention. It also noted no significant difference in pain reduction between Alvogyl and SaliCept, recommending SaliCept as a suitable alternative to Alvogyl in the management of AO.

Chaurasia[46] compared the effectiveness of zinc-oxide eugenol and Alveogyl in the management of AO and found that zinc-oxide eugenol is significantly more effective in terms of pain management compared to Alveogyl.

An RCT by Burgoyne[50] assessed the efficacy of topical anaesthetic gel in terms of pain relief for AO but found no significant difference compared to eugenol.

An RCT by Yuce and Komerik[44] compared the use of saline irrigation versus PRF and found mean pain score was significantly lower in the PRF group. Soft tissue healing was also significantly faster.

Discussion

The aim of this scoping review was to provide a comprehensive overview of the literature relating to the aetiology, prevention and management AO and highlight the burden of un-necessary antibiotic prescribing and extent of inappropriate use of intra-alveolar chlorhexidine. In keeping with previous literature, the incidences noted ranged from 0% to 38%, with most incidences in the 0.0-5.0% range. Studies mostly assessed AO incidence in

secondary care and does not account for the large number of extractions, and potentially AO complications, that arise in primary care. Of the included studies, surgical protocol varied widely. Of particular concern, 18 papers included for review routinely prescribed antibiotics pre-, peri-, or post-operatively, or to manage diagnosed AO. As detailed in this review, the use of antibiotics in the prevention or management of AO is inappropriate, unjustified and adds to the global threat of anti-microbial resistance. In addition to this, 14 studies reported use of intra-alveolar chlorhexidine, exposing patients to serious risk of anaphylaxis.

Aetiology:

With regards to the aetiology, recent evidence appears to be conflicting. The results of Letivin[6] suggest that impaired immune function may increase the risk of developing AO. It is suggested in the paper that the immune factors for clotting may not be present or sufficient in immune-compromised patients, placing them at higher risk for the development of AO. This may provide a physiological mechanism for the development of AO with regards to the absence of fibrin clot formation. With regards to increasing age, Adeyemo[8] concluded that age is not a significant risk factor, however the study compared 470 patients <40years of age with 36 patients >40years of age. This may account for the different incidences in AO seen in the two groups, and it is questionable as to whether the two groups are comparable due to the disparity in sample sizes. Most studies in this review have a mean age in the 30-40year age bracket. Further studies focussing on older (>50-60yrs) should be carried out to fully assess the impact of increasing age on the risk of developing AO, especially given the currently increasingly ageing, dentate population.

Interestingly, in terms of smoking, 4 papers[17,37,24,25]concluded that smoking is not a significant risk factor in the development of AO, while Elo[10] found smoking to be associated

with a significantly higher incidence of AO. According to current UK guidelines, patients are advised to not smoke for 24-72 hours following exodontia to reduce the risk of AO, with the RCS[5] recommending cessation of smoking for 2 weeks. This can be a stressful and often un-achievable instruction for patients to follow and may be a factor in delaying access to routine exodontia potentially leading to more pain and severe infection, and the need for more extensive future intervention. Smoking is known to cause impaired oral wound healing through vasoconstriction within the oral cavity causing localised ischaemia. Cigarettes also contain a number of chemicals which may play a role in AO development. These factors may contribute to the aetiology of AO however the exact mechanism of how smoking would be linked to the development of AO is currently unclear in the literature. Given the prevalence of smoking and the proposed aetiology of impaired blood clot formation, there is need for a high-quality randomised-controlled-trial to assess the impact of smoking on the incidence of AO, with participants matched for age, gender, and other lifestyle factors. No papers to date specifically assess the relationship between electronic cigarette use and the incidence of AO. E-cigarette use is increasingly popular and may have implications for oral health and soft-tissue health following exodontia and is something that should be examined in a large RCT in more detail to gain further understanding of its implications.

There is conflicting evidence that surgical technique may influence the development of AO – Abu-Mostafa[51] noted that root separation significantly increased AO incidence. Mohajerani[9] noted a reduction in AO with modified triangular flap, in contrast to 4 other papers[10,67,68,69] which found no significant difference. 2 papers[25,37] noted a significant association between difficulty of extraction and AO. These factors are based on technique and operator skill as opposed to physiological factors which may place patients at higher risk of developing AO, and as such are more relevant for clinicians to be aware of when carrying out exodontia.

Prevention:

In terms of prevention, the use of PRF was found to be effective by 3 out of 6 papers[35,37,55], suggesting it may be a useful prophylactic intervention post-extraction in the prevention of AO and wound healing complications, however it is a relatively new intervention and further investigation into its effectiveness in the form of high-quality RCT's is required.

Management:

In terms of a reduction in pain and soft-tissue inflammation, hyaluronic acid[43,47] and low-level laser therapy appear to be effective interventions[48,49].

Alveogyl, which is eugenol based, is commonly used in primary and secondary care settings in the UK in the management of AO and has long been the first-line treatment of choice in the management of AO. In 2012 for the UK, Alvogyl was re-formulated by the manufacturer, removing two of the three active ingredients - idioform (antimicrobial) and butamben (anaesthetic). The product name was changed to Alveogyl, with eugenol listed as the only active ingredient. The packing remained largely unchanged. The re-formulation was due to the MHRA highlighting the potential for adverse reactions and the risk these posed to patient safety. The authors were unable to find any formal announcement of this change from the manufacturer and all studies relating to the effectiveness of this product as a standalone treatment appear to be based on Alvogyl, not Alveogyl. No papers included in this review make reference to the change in formula. In the literature, only two papers appear to highlight this change[71,72]. In a letter to the editor, Kalsi et al[71] conducted a survey of 120 UK dentists and found that 56% were unaware of the name change, with 91% unaware of the

changes to the formula. In addition to this, the SDCEP guidelines[59], updated in 2018, still recommend Alvogyl as the treatment of choice despite its lack of availability in the UK.

The evidence in this review suggests that, when compared to both Alvogyl and Alveogyl, zinc oxide eugenol; hyaluronic acid; low-level laser therapies and PRF are more effective in terms of pain reduction and inflammation management for AO. It is unlikely that dentists in general practice will have access to laser therapies, and as such a treatment choice of HA, PRF or ZnOE will likely depend on the availability of these products in individual practices.

Inappropriate prescribing and chlorhexidine use:

Dental prescribing accounts for up to 8% of antibiotic prescriptions in England[61] and as of 2015, dentists have a statutory responsibility to ensure antibiotics are prescribed appropriately in order to reduce the burden of antimicrobial resistance[62]. As noted in this review, there is little recent evidence to support the use of antibiotics in relation to AO in the majority of cases. One study included in this review noted the number needed to treat to prevent a single AO case to be 40[20]. Given the number needed to treat is so high, consideration should be given to the inappropriate nature of prescribing antibiotics prophylactically in light of increasing antimicrobial resistance and serious adverse reactions. Despite this, and the SDCEP guidelines[59] not advocating for it, in the literature it is noted that it is still common practice to prescribe antibiotics to prevent and manage AO[63], with up to half of UK dentists considering antibiotics to be an appropriate intervention in the management of AO[64]. The RCS National Clinical Guidelines[5], which advocate for the use of prophylactic antibiotics for AO, also likely serve to confuse clinicians in the decision-making process.

Chlorhexidine has long been the gold-standard rinse and gel within dentistry, particularly with regards to the prevention and management of AO. General oral chlorhexidine use can

result in a number of side effects such as alterations to taste sensation, staining of dental hard tissues and irritation to oral mucosa. In addition to this, direct socket irrigation has more recently been associated with two cases of fatal adverse reactions as a result of hypersensitivity[60]. The studies included in this review[23,52,53,56] agree with a 2012 Cochrane review which concluded that chlorhexidine use has some benefit in the prevention and management of AO[65].

However, given there is a recent history of fatal adverse reactions, the benefits of chlorhexidine use do not outweigh the risks of intra-alveolar use. The studies included in this review and in recent general literature fail to highlight the small but plausible risk of serious adverse reactions and its use is still widespread within primary and secondary care. Saline irrigation and eugenol pastes have been shown to be equally as effective as chlorhexidine in reducing the incidence of AO[27,31,40,54]. These are potential alternative interventions that could be used to prevent the development of AO that are safe, cheap and readily available in primary and secondary care. Given the current emerging evidence of developing hypersensitivity to chlorhexidine, saline should replace chlorhexidine as the intra-alveolar irrigant of choice in the prevention and management of AO. The use of intra-alveolar chlorhexidine should be considered inappropriate given the small but serious risk to patient safety posed by its use, and clinicians should be mindful of this, and the evidence regarding the effectiveness of saline, when considering how to prevent and manage AO.

Future research:

This review has highlighted the lack of understanding surrounding the pathophysiology of AO. This scoping review had some limitations. Many studies included did not publish raw data, and surgical protocol varied widely. As such, this scoping review provides an overview of the wide range of concepts relating to alveolar osteitis that have currently been

investigated. Furthermore, this was a large review and as such our results are only up to date as of March 2020. Further understanding of the mechanism by which AO occurs will help in understanding the aetiology of the condition. To investigate aetiology, large, high-quality RCT's, or alternatively long-term observational studies are required. Once some insight into the aetiology is gained, it would be of benefit to carry out further studies into the prevention and management of the condition, targeted towards 'at risk' groups identified from aetiological evidence. It may be beneficial in 'at risk' groups to carry out preventive interventions post-exodontia, for example saline irrigation or the use of PRF to prevent AO development and repeated return visits to primary or secondary care, as well as avoidance of a painful condition for the patient. In addition to this, studies assessing the altered formulation of Alveogyl should be undertaken and included in the evidence based to aid the formulation of national clinical guidelines to standardise safe, effective and evidence-based clinical practice.

Conclusion

The development of consistent, evidence-based, up-to-date protocols or guidelines are needed to assist clinicians in both primary and secondary care, including the need for general practitioners to be mindful of the risks to patient safety posed by inappropriate use of intra-alveolar chlorhexidine and un-justified antibiotic prescribing, and to utilise saline as their irrigant of choice to prevent and manage this common, painful condition thus reducing risks to patients from anaphylaxis and reducing the global burden of AMR. As operator skill and technique appears to influence the development of AO, clinicians should be mindful of an atraumatic, careful surgical technique when performing exodontia. With regards to management, UK clinicians should be aware of the formulation changes to Alveogyl and the lack of studies relating to the new formulation. Local measures should be considered as the

gold-standard for management. This should include saline irrigation and the use of PRF, HA, or ZnOE, as well as the avoidance of antibiotic prescribing in the absence of signs of infection. Advice should be given regarding suitable at-home analgesia for the individual. Patients should be offered a 2-week review appointment in order to monitor healing and address any concerns.

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Figure Legend

Label	Description
Figure 1	PRISMA flow diagram detailing number of papers returned by initial search, abstract exclusions, full text exclusions and number of papers included for review
Figure 2	Graph to show the aetiological factors proposed by the included papers and their significance with P=0.05
Figure 3	Graph to show the preventive interventions proposed by the included papers and their significance with P=0.05
Figure 4	Graph to show the management options proposed by the included papers and their significance with P=0.05

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