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Review

Management of Medication-Related Osteonecrosis of the Jaw: An Overview of National and International Guidelines

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Abstract

There is variability amongst clinicians in the management of medication-related osteonecrosis of the jaw (MRONJ) though numerous guidelines are available. The aim of this critical review is to appraise current international and national guidelines on MRONJ to evaluate areas of consensus or inconsistency, identify areas lacking evidence, and discuss recommendations with agreement and variability across guidelines. A literature search was performed to identify all national and international guidelines published until May 2022 on the prevention and treatment of MRONJ. Included guidelines were compared and critically appraised with Appraisal of Guidelines for Research and Evaluation II (AGREE II). The included sixteen guidelines were published from ten different countries, two of which had international collaborations. AGREE II assessment found four guidelines of high quality. There is consensus to optimise oral health prior to and during therapy, to conservatively manage established MRONJ in earlier stages and consider surgery at advanced stages. There is disparity on strategies to reduce the risk of osteonecrosis such as the avoidance of invasive dental procedures, therapy suspension, and techniques to reduce the impact of invasive surgery. The authors recommend an international lead in the development of dental guidelines to establish a global standardised management approach aiming for better health equality.

Keywords: MRONJ; Bisphosphonates; Denosumab; Antiresorptive; Antiangiogenics; Guidelines

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious complication from antiresorptive and antiangiogenic therapy, causing progressive bone destruction in the maxillofacial region.[1] Patients can present with multiple oral complaints impacting negatively on their quality of life.[2] The first cases of osteonecrosis of the jaw were reported in 2003 in relation to two bisphosphonates, pamidronate and zoledronate.[3] Over time other medications including denosumab and medications with antiangiogenic effects, such as tyrosine-kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF) inhibitors, and mammalian target of rapamycin (mTOR), have been reported to cause osteonecrosis.[1,4–6] The benefit of these medications on managing the primary disease can be significant, therefore the prevention and treatment of MRONJ is vital.

The pathogenesis of the MRONJ is not fully understood and therefore assessing the risk, preventing, and managing MRONJ is challenging. Suppression of bone turnover and angiogenesis inhibition are suggested mechanisms of MRONJ through reduction of osteoclast function and apoptosis, however, increased osteoclast function has been observed in samples of necrotic bone.[7] Antiresorptive and antiangiogenic agents affect immune system surveillance and healing through impairment of neutrophils, monocytes, and keratinocytes.[8] The dysfunction of macrophages can cause prolonged inflammation favouring the oral environment to pathogenic microorganisms.[9] The exact role of

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microorganisms is yet to be determined thus the use of antimicrobial agents is not supported by theory or clinical evidence.[10]

Diagnosis is based on patients' symptoms and clinical signs. Histological and radiological investigations can be non-specific and could delay recognition of early disease.[4] MRONJ diagnosis is based on five stages. The initial stage is described as 'at risk' with no signs or symptoms in patients on antiresorptive or antiangiogenic therapy. Stage 0 describes a non-exposed variant, and subsequent stages 1 to 3 describe exposure of bone with worsening symptoms and structural involvement. Treatment is based on the stage of disease for a universal approach, thus accuracy of the diagnosis is important for the correct management.[1] Dentists have a significant role in identifying patients at risk of MRONJ, providing preventative strategies and recognising MRONJ.[11]

Several guidelines have been developed to address the management of MRONJ and compliance with guidelines should improve patient outcomes. Yet clinicians are uncertain in strategies to reduce risk and prevent MRONJ as well as treating established disease. Our study aims to review the available guidelines, assess their quality, identify areas lacking evidence, and discuss recommendations with agreement across guidelines and recommendations that vary between guidelines.

Methodology

Study design

An electronic literature search for guidelines relating to the management of MRONJ was undertaken. The obtained guidelines were assessed and recommendations compared in relation to the prevention and treatment of MRONJ. The outcomes were identified in areas of consistency, variability, and limited knowledge. The guidelines were critically appraised using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) to evaluate their strength.

Literature search and selection

An electronic literature search, using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) tool, was completed on PubMed, National Institute of Health, and Care Clinical Excellence (NICE), Guideline Central, Turning Research into Practice (TRIP) database, and Google Scholar for guidelines only (Fig. 1). A manual search through the reference list of the included guidelines was also performed. Search strategy terms were used to capture relevant guidelines (Supplemental Table 1, online only).

Articles were screened by title, then abstract, and subsequently by full text. Inclusion criteria included: 1) guidelines

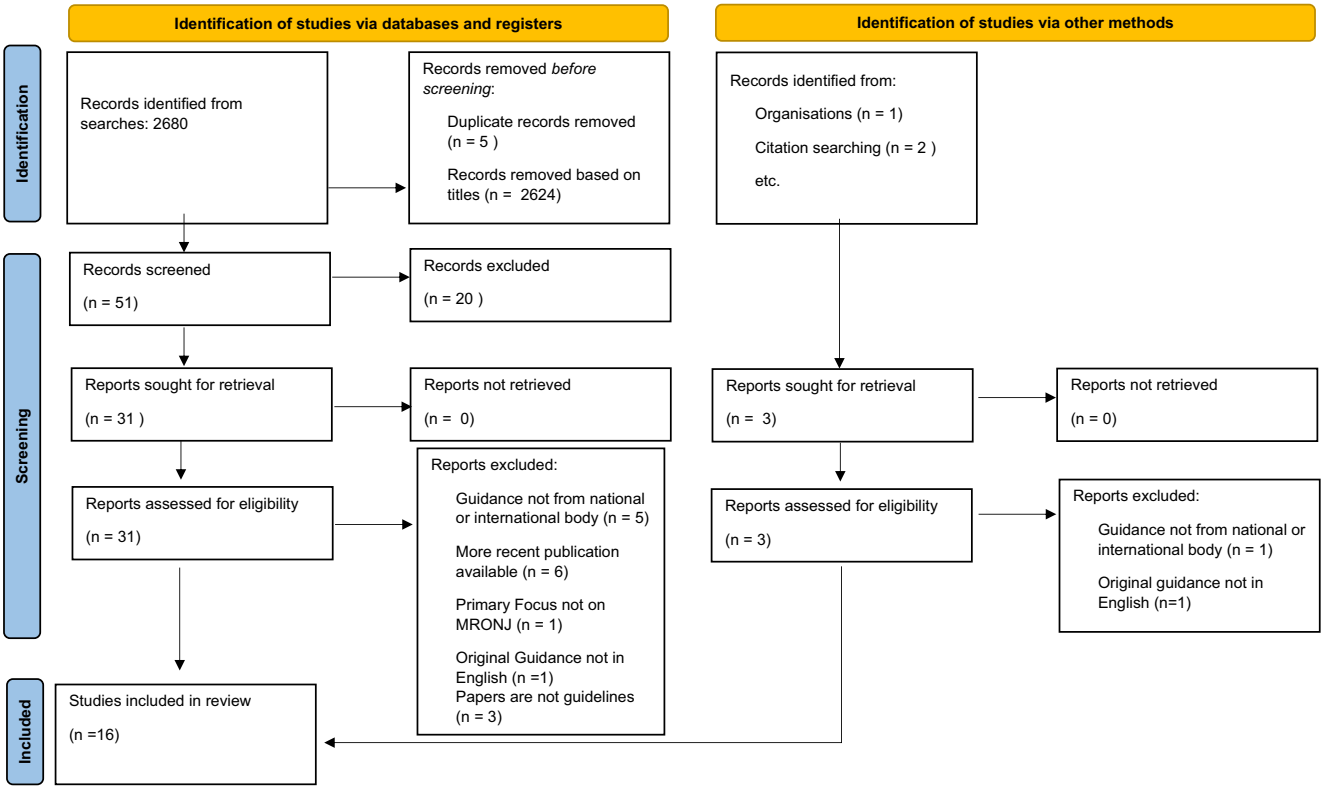

Fig. 1. PRISMA diagram of search strategy.

on prevention and treatment of MRONJ; 2) international and national guidelines in the English language only, but no publication date restrictions were applied. Exclusion criteria included: 1) guidelines with irrelevant scope to the research question; 2) guidelines not affiliated with a national or international body such as those developed at a local level; 3) the most up to date guidelines from the same national or international body were selected.

Quality assessment

The included guidelines were critically appraised using AGREE II. AGREE II assesses the guidelines in seven domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. An overall score out of 7 was given to the guideline. A guideline score of 0 to 2 was considered of low quality, 3 to 4 moderate and 5 or more was deemed high quality.

Data extraction and analysis

A benchmark guideline was selected based on a high AGREE II score and recommendations to encompass prevention and treatment of MRONJ. Other included guidelines were then compared with the benchmark guideline for consensus. Consensus was calculated as percentage with; 0–30% set as weak, 31–60% moderate and 61% or more as strong. The below data were extracted from all included guidelines: author and year; patient cohort based on primary disease or risk; recommendations for prevention of MRONJ prior to and during therapy; recommendations for the management of MRONJ; data on level of evidence.

Quality assurance

This is a critical review conducted adopting the systematic review methodology to ensure good quality and reduce the potential for introducing literature search bias. The literature search, selection, data extraction and critical appraisal were undertaken by one author (NP), checked, and agreed by the second author (NS). Furthermore, this review was peer reviewed and assessed by internal and external examiners at one of the UK-based universities as part of a master's degree study.

Results

Study selection and characteristics of included guidelines

The electronic search identified 31 guidelines and three guidelines were found through manual searches. Inclusion

Table 1a
Summary of included Guidelines with description of their primary body, aim, targeted user and Staging system if used and AGREE II Score

Primary Body (Nation)/Author	Year	Population/ (Medication)	Objective	Target User	Staging Criteria	AGREE II Score
AAOMS (USA) *Ruggiero et al 2022*[S1]	2022	Non-Cancer and Cancer (Antiresorptive Agents)	Prevention and Treatment	Health Care Professionals and Organisations	AAOMS	4
KSBMR/KAOMS (South Korea) *Kim et al 2021*[2]	2021	Osteoporosis (Antiresorptive Agents)	Prevention and Treatment	Medical and Dental Professionals	AAOMS modified (no stage 0)	3
ACOMM (Columbia) *Chalem et al 2020*[S3]	2020	Non-Cancer and Cancer (All medication at risk)	Prevention and Treatment	Health Care Professionals	AAOMS	5
SBEM/SOBEP/ABRASSO (Brazil) *Madeira et al 2020*[S4]	2020	Osteoporosis (Antiresorptive Agents)	Prevention and Treatment	Health Care Professionals	Not used	3
MASCC/ISOO/ASCO (USA/International) *Yarom et al 2019*[S5]	2019	Cancer (Antiresorptive Agents)	Prevention and Treatment	Cancer Care Team, Dentists, Dental Specialists	AAOMS	6
UK Chemotherapy Board (UK)[S6]	2019	Cancer (All medications at risk)	Prevention and Treatment	Oncology MDT	AAOMS	3
SIPMO (Italy) *Di Fede et al 2018*[S7]	2018	Non-Cancer and Cancer (Antiresorptive and Antiangiogenic Agents)	Prevention	Dentists and Hygienists	N/A	3
JSBMR (Japan) *Yoneda et al 2017*[S8]	2017	Non-Cancer and Cancer (Antiresorptive Agents)	Prevention and Treatment	Physicians, Oral Surgeons Dentists	AAOMS	3
SDCEP (UK)[S9]	2017	Non-Cancer and Cancer (Antiresorptive and Antiangiogenic Agents)	Prevention	Dentists (Primary Care)	N/A	7
ASBMR (USA/International) *Khan et al 2015*[S10]	2015	Non-Cancer and Cancer (Antiresorptive Agents)	Prevention and Treatment	Health Care Professionals	ASBMR	5
AAE (USA) *Goodell and Balson 2012*[s11]	2012	Non-Cancer and Cancer (Bisphosphonates)	Prevention	Dental Professionals	N/A	2
ADA[1] Scientific Affairs (USA) *Hellstein et al 2011*[S12]	2011	Osteoporosis (Antiresorptive Agents)	Prevention and Treatment	Oral Health Care Professionals	AAOMS	3

and exclusion criteria were applied to the 34 guidelines and a total 16 were included for the study (Fig. 1, Supplement Table 2 for references online only).

The included guidelines are published between 2005 and 2022 from national bodies associated with eleven countries, with two guidelines associated with international associations. All sixteen papers made recommendations on the management of antiresorptive agents of which, four discussed management of non-antiresorptive agents.[S1-S4] The target populations included were those treated for cancer and those treated for non-malignant disease, primarily osteoporosis. All the guidelines aimed to make recommendations on the prevention of MRONJ. Eleven included recommendations for treatment (Table 1).[S1, S2, S5-S10, S12-S14]

AGREE II assessment

The overall quality of the guidelines was low to moderate (Table 1). Four guidelines scored 5 or more that we considered for this study to be of high quality.[S1, S4, S8, S10] The Clinical Practice Guideline by Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) was selected as the benchmark guideline.[S8] Across the guidelines domains of 'Scope and purpose' and 'Clarity of presentation' scored highly. 'Rigour of development,' 'Editorial independence' and 'Applicability' were low scoring amongst weaker guidelines (Supplemental Table 3, online only).

Risk factors

Recognised risk factors were grouped into risks associated with the antiresorptive medication, oral risk factors and patient systemic risk factors. There was a strong consensus in identified oral risk factors and risk associated with antiresorptive agents. There was strong consensus for corticosteroids, angiogenic inhibitors and diabetes as significant risk factors but varying agreement in other patient risk factors (Table 2).

Prevention prior to therapy

There is a strong agreement between the included guidelines that a dental assessment should be undertaken prior

Table 1b
Summary of included Guidelines with description of their primary body, aim, targeted user and Staging system if used and AGREE II Score

Table 1b: Summary of included Guidelines with description of their primary body, aim, targeted user and Staging system if used and AGREE II Score

Primary Body (Nation)/Author	Year	Population/ (Medication)	Objective	Target User	Staging Criteria	AGREE II Score
German Society of Senology (Germany) *Fehm et al 2009*[S13]	2009	Breast Cancer (Bisphosphonates)	Prevention and Treatment	Health Care Professionals	Not stated	3
CAOMS (Canada) *Khan et al 2008*[S14]	2008	Non-Cancer and Cancer (Bisphosphonates)	Prevention and Treatment	Medical and Dental Practitioners, Oral Pathologists, and related Specialities	CAOMS	4
ANZBMS/OA/MOGA/ ADA[2] (Australia/New Zealand) *Sambrook et al 2006*[S15]	2006	Non-Cancer and Cancer (Bisphosphonates)	Prevention	Medical and Dental Practitioners	N/A	2
AAOM (USA) *Migliorati et al 2005*[S16]	2005	Non-Cancer and Cancer (Bisphosphonates)	Prevention	Dental Practitioners	N/A	3

Abbreviations: AAE – American Association of Endodontics, AAOM – American Academy of Oral Medicine, AAOMS – American Association of Oral and Maxillofacial Surgeons, ABRASSO – Brazilian Association for Bone Evaluation and Osteometabolism, ACOMM – Columbian Association of Osteoporosis and Mineral Metabolism, ADA[1] -American Dental Association, ADA[2] – Australian Dental Association, ANZBMS – Australia and New Zealand Bone Mineral Society, ASBMR – American Society of Bone and Mineral Research (International Task Force on Osteonecrosis of the Jaw), ASCO – American Society of Clinical Oncology, CAOMS – Canadian Association of Oral and Maxillofacial Surgeons, GSS – German Society for Senology, ISOO – International Society of Oral Oncology, JSBMR – Japanese Society of Bone and Mineral Research, KAOMS – The Korean Association of Oral and Maxillofacial Surgeons, , KSBMR – The Korean Society of Bone and Mineral Research, MASCC – Multinational Association of Supportive Care in Cancer, MOGA – Medical Oncology Group of Australia, OA – Osteoporosis Australia, SBEM – Brazilian Society of Endocrinology and Metabolism, and Oral Pathology, SDCEP – Scottish Dental Clinical Effectiveness Programme, SIPMO – Italian Society of Oral Pathology and Medicine, SOBEP – Brazilian Society of Stomatology.

KEY – High Quality (Green), Moderate Quality (Yellow), Low Quality (Red)

Abbreviations: AAE – American Association of Endodontics, AAOM – American Academy of Oral Medicine, AAOMS – American Association of Oral and Maxillofacial Surgeons, ABRASSO – Brazilian Association for Bone Evaluation and Osteometabolism, ACOMM – Columbian Association of Osteoporosis and Mineral Metabolism, ADA[1] -American Dental Association, ADA[2] – Australian Dental Association, ANZBMS – Australia and New Zealand Bone Mineral Society, ASBMR – American Society of Bone and Mineral Research (International Task Force on Osteonecrosis of the Jaw), ASCO – American Society of Clinical Oncology, CAOMS – Canadian Association of Oral and Maxillofacial Surgeons, GSS – German Society for Senology, ISOO – International Society of Oral Oncology, JSBMR – Japanese Society of Bone and Mineral Research, KAOMS – The Korean Association of Oral and Maxillofacial Surgeons, , KSBMR – The Korean Society of Bone and Mineral Research, MASCC – Multinational Association of Supportive Care in Cancer, MOGA – Medical Oncology Group of Australia, OA – Osteoporosis Australia, SBEM – Brazilian Society of Endocrinology and Metabolism, and Oral Pathology, SDCEP – Scottish Dental Clinical Effectiveness Programme, SIPMO – Italian Society of Oral Pathology and Medicine, SOBEP – Brazilian Society of Stomatology.
KEY – High Quality (Green), Moderate Quality (Yellow), Low Quality (Red)

Table 2
Risk factors of MRONJ and prevention strategies prior to and during antiresorptive therapy with guideline consensus agreement (%) between guidelines.

Oral Risk Factors		**Patient Risk Factors**	
Poor Oral Hygiene	56% (9/16)	Diabetes	63% (10/16)
Invasive Dental Treatment	100% (16/16)	Smoking	50% (8/16)
Ill-fitting prosthesis	63% (10/16)	Angiogenic Inhibitors	63% (10/16)
Inflammation/Infection	81% (14/16)	Chemotherapy	31% (5/16)
		Corticosteroids	69% (11/16)
Risk Associated with Antiresorptive Medication		Renal Disease	31% (5/16)
Duration	81% (14/16)	Erythropoietin Therapy	25% (4/16)
Type	63% (10/16)	Rheumatoid Arthritis	38% (6/16)
Dosage	75% (12/16)	Immunosuppressant's	19% (3/16)
Indication	75% (11/16)	Anaemia	25% (4/16)
		Age	38% (6/16)
		Genetics	25% (4/16)

Prior to commencing antiresorptive therapy				
Indication	Cancer		Non-Cancer (Osteoporosis)	
Dental Assessment	If non-urgent therapy required, then essential	100% (13/13)	Before commencing or complete within 6 months	92% (12/13)
Aim of Assessment	Oral Hygiene Instruction and Patient Education regarding risks of MRONJ and Risk Factors			81% (13/16)
	Full Dental Assessment (including periodontal disease, prosthesis, radiographs) and manage teeth of poor prognosis			88% (14/16)
Begin Therapy	Once Mucosal Healing Complete			31% (5/16)

During therapy with antiresorptive agent			
Dental Follow Interval of 3 – 6 months	69% (11/16)	Promote OH and reduce risk factors	69% (11/16)
Avoidance of Invasive Dental Procedures	50% (8/16)	Antiseptic/Antimicrobial Prophylaxis prior to invasive treatment	63% (10/16)
Drug Holiday for Invasive Treatment with discussion with prescriber	38% (6/11)	Primary wound closure for extractions +/- alveoplasty	38% (6/16)
Regular Professional Hygiene Appointments	25% (4/16)	Regular Panoramic Radiographs	13% (2/16)

to the initiation of antiresorptive therapy. All guidelines recommended patients with cancer required a dental assessment prior to antiresorptive therapy.[S1-S5, S8-S11, S13-S16] Only one guideline did not suggest a dental assessment prior to therapy in non-cancer cases.[S11] The aims of prevention were recorded in thirteen guidelines as to optimise oral hygiene, educate patients regarding MRONJ and reduce risk factors.[S1-S6, S8-S10, S12-S16] In relation to the dental assessment fourteen guidelines of the sixteen were explicit in stating a full dental assessment was required including the assessment of periodontal tissues, prosthesis, and radiographs with the aim to manage teeth of poor prognosis (Table 2).[S1-S3, S5, S6, S8-S10, S12-S16]

Prevention during therapy

Once antiresorptive therapy has been established, regular dental review at least every three to six months and promotion of good oral hygiene and reduction of risk factors was recommended in eleven guidelines.[S1-S6, S8-S10, S12, S13] During the maintenance period, recommendations to have professional hygiene appointments and regular panoramic radiographs were of low consensus. A statement to avoid invasive dental procedures was given in eight of the guidelines.[S1, S2, S5, S9, S11, S13, S15, S16], However, three guidelines stated that invasive dental procedures to eliminate inflammation or infection should not be delayed if non-surgical means are not feasible.[S3, S4, S6] When extractions are required, antiseptic and antimicrobial prophylaxis is advised in ten guidelines.[S1, S3, S7-S10, S12, S13, S15, S16] In addition to this, a drug holiday from the antiresorptive medication was recommended in six guidelines at the prescribing physician's discretion.[S1, S6, S9, S10, S14, S16] Six guidelines advised primary closure of the dental socket, with or without alveoplasty (Table 2).[S1, S3, S7, S9, S13, S15]

Treatment of MRONJ

Seven guidelines used a staging-system-based approach to treatment set out by American Association of Oral and Maxillofacial Surgery (AAOMS) in 2014 where conservative management is recommended in earlier stages and surgery for refractory or severe diseases.[1] The use of stage 0 had a moderate consensus with five guidelines suggesting its use.[S1,S3,S5,S6,S8] Five guidelines recommended discussion with the prescribing physician to consider a drug holiday from antiresorptive therapy (Table 3).[S3, S8-S10, S14]

Discussion

Prevention: prior to antiresorptive therapy

Areas of consensus

Dental assessment prior to antiresorptive therapy. There is agreement amongst the guidelines that a dental assessment should be undertaken prior to the initiation of antiresorptive therapy. Considering the first cases of osteonecrosis of the jaw (ONJ) were preceded by dental extractions, the aim of the initial assessment has been to eliminate future need for invasive treatment.[S14, S15,12]

The level of assessment prior to initiation of antiresorptive therapy should be comprehensive including the evaluation of the prosthesis, periodontal tissues, and use of radiographs to understand the oral health status of the patient.[S6, S8, S12, S16,13] Studies have shown that the incidence of MRONJ is reduced by 77.3% by undertaking these measures.[12,14] As cancer patients have a higher risk of developing MRONJ, a dental assessment prior to therapy is essential if the need for antiresorptive therapy is not immediate.[15] Furthermore, the dental intervention can be more radical as the risk increases after a year.[16] Patients with osteoporosis have a lower risk of MRONJ as antiresorptive agents are administered at lower doses and less frequently.[1] Thus, the dental assessment can be undertaken within six months of initiating therapy.[S5, S9, 17]

Anti-angiogenic therapy, corticosteroids and diabetes are the most common patient risk factors, and these factors are strongly agreed between guidelines. However, there is a degree of variability between guidelines on other patient risk factors due to limited evidence based on retrospective case series or case cohort studies.[4,5] There is a consensus that duration of treatment is also a risk factor. Guidelines suggested treatment for two to five years may increase risk, but observational studies for patients with osteoporosis on bisphosphonate treatment highlighted minor change over ten years, thus a more accurate record of exposure is required along with consideration of additional risk factors.[S5]

Areas of variability

Initiation of therapy following initial dental assessment. There is variation between the guidelines as to when antiresorptive therapy can begin after the initial assessment and dental

Table 3
Treatment of MRONJ based on staged approach with guideline consensus agreement (%)[1, S5].

Treatment of MRONJ		
Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.		
Stage	Treatment	
At Risk- No apparent necrotic bone in asymptomatic patients who have been treated with IV or oral antiresorptive or antiangiogenic therapy	No treatment indicated. Patient education	63% (7/11)
Stage 0/Increased Risk - No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms	Antibacterial mouth rinse Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to prescriber. Patient education and reduction of modifiable risk factors	46% (5/11)
Stage 1 - Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection	Symptomatic management, including the use of pain medication and scrutiny and follow up Refer to dental specialist and follow up every 8 weeks with communication of lesion status to the prescriber Patient education and reduction of modifiable risk factors	76% (8/11)
Stage 2 - Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Symptomatic treatment with oral antibiotics and topical antibacterial rinse Pain control Debridement to relieve soft tissue irritation and infection control. Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to prescriber. Patient education and reduction of modifiable risk factors	76% (8/11)
Stage 3 - Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone,(i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor	Symptomatic treatment with oral antibiotics and topical antibacterial rinse Pain control Surgical debridement or resection for long-term palliation of infection and pain Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to prescriber. Patient education and reduction of modifiable risk factors	63% (7/11)
Suggestion of therapy suspension to aid treatment of MRONJ with discussion with prescriber (variable period of therapy suspension)		46% (5/11)

intervention. Some suggest two weeks until mucosal healing whilst others suggest up to eight weeks for complete healing.[S3, S12] For patients having undergone invasive dental treatment prior to head and neck radiotherapy, ideally 10 to 14 days should be allowed for sockets to heal.[18] However, the urgency of antiresorptive therapy will influence when the treatment could be initiated and as such, communication with the prescribing physician is essential.[S2, S7, S8,13]

Summary

All patients commencing antiresorptive therapy should have a dental screen and optimisation of dental health. In low-risk cases this can be completed within six months of therapy starting. There is no consensus as to when therapy can start following dental intervention, thus communication with prescriber is important to ensure adequate time is given to healing and avoidance of delay for primary treatment.

Prevention: during antiresorptive therapy

Areas of consensus

Prevention protocol during antiresorptive therapy. Regular dental visits between three to six months during which time the continuing promotion of oral hygiene and reduction of risk factors is strongly agreed by guidelines.[S1-S6, S8-S10, S12, S13] Enhanced preventative measures every three months in high-risk patients appeared to reduce incidence of MRONJ.[14,19] Most studies relate to high-risk patients on IV bisphosphonates or under treatment for cancer, which suggests that enhanced prevention would be significantly more effective in these cases.[12]

Antimicrobial prophylaxis prior to invasive procedures. Despite lack of supporting evidence, the use of antiseptic and antimicrobial prophylaxis was recommended in several guidelines using varying protocols, which is confusing. The strength of evidence for prophylaxis is low as a systematic review found significant heterogeneity between observational studies and a lack of randomised control trials.[20] The Faculty of General Dental Practitioner Guidelines (FGDP) and the Scottish Dental Effectiveness Guidelines are nationally recognised standards in the UK for general dental practitioners, and do not recommend antibiotic prophylaxis.[S4, S8, 21,22]

Areas of variability

Regular professional hygiene appointments. Periodontal disease was the second most observed dental comorbidity. Four guidelines highlighted, if necessary, the need for regular professional cleaning.[S2, S3, S6, S8] Periodontal disease has preceded cases of MRONJ; however, studies have been based on limited numbers of patients and had no adjustment of confounding factors.[23] Professional cleaning is not contraindicated in cancer or non-cancer patients and can be provided to reduce inflammation if necessary.[S3, 24]

Periodic panoramic radiographs. Two guidelines suggested regular panoramic radiographs for patients at risk of MRONJ.[S7, S10] The early changes of MRONJ on panoramic film are difficult to identify in contrast to established necrosis, which were more easily identifiable.[25] A systematic review highlighted the use of a pretherapy panoramic film that can be used as reference for future changes.[26] However, the authors suggest that radiation exposure and accessibility of the modality across a population should be taken into consideration.

Drug holiday prior to invasive treatment. There is varied consensus for a drug holiday prior to invasive therapy with six guidelines stating a potential benefit to healing.[S1, S3, S7, S9, S13, S15] One trial of cancer patients compared a drug holiday for dentoalveolar surgery against no holiday and found there was an increased risk of cancer progression and cases of MRONJ in the drug holiday group.[27] A systematic review highlighted the lack of high-level evidence of a high dose drug holidays and outcomes were inconsistent.[28] Denosumab has a limited half-life and in the lower dosages for osteoporosis, invasive procedures could be undertaken between three and four months following the last dose.[S5] In cases of high dose denosumab, a study found a drug holiday did not change the risk of MRONJ, but modifying other factors, such as oral hygiene, were more important.[29]

Primary closure and alveoplasty. An elective alveoplasty and primary closure following dental extraction were recommended in several guidelines to reduce risk of MRONJ.[S3, S7, S9, S10, S16] Several studies demonstrated low or no incidence of MRONJ with primary closure. However, these studies did not include a control group and had enhanced preventative measures prior to treatment, thus the evidence to support this is unclear.[19]

Avoidance of invasive procedures. There is mixed consensus as to the avoidance of invasive procedures. As understanding of risk has improved, caution should be given to primarily high-risk groups.[S4, S8, S11, S16] Where possible non-invasive treatment, which avoids insult to the alveolus, should be performed with patients at higher risk, but invasive treatment in the presence of infections should not be delayed. A retrospective observational study demonstrated early extraction of an infected tooth had lower incidence of MRONJ than a delayed extraction.[30] This is reflected in one guideline in which invasive treatments, such as extractions, periodontal surgery, and endodontic surgery, are indicated to manage infection or inflammation.[S3] No consistent strategy is provided by guidelines to reduce the risk of MRONJ in patients with higher risk.

Summary. Regular dental examinations and promotion of oral hygiene is recommended for patients at risk of MRONJ with increased frequency up to three-monthly for those with recognised risk factors. There is variability in the approach to avoid invasive procedures but when indicated to manage infection this should not be delayed. Strategies to reduce risk from invasive treatment remain unclear. Preference should

be given to non-invasive management for those at substantial risk.

Treatment of MRONJ

Areas of consensus

Treatment based on MRONJ staging. Yarom et al[S8] followed a conservative approach for preliminary stages based on formal consensus. Preference for conservative management was based on the risk of invasive surgery causing further necrosis and encouraging the formation of removable sequestra.[31] However, a surgical approach can have a predictable outcome in a shorter period in all stages when compared to non-surgical measures.[32,33] Ruggeiro et al[S5] provides an equal approach to surgery and conservative management based on clinical situation and patient factors. There is unclear evidence from randomised controlled trials to support conservative or surgical measures.[34]

Conservative management involves the provision of antimicrobial therapy to control and treat infection at the area of necrosis.[35,36] In the included guidelines there was no clear protocol, due to limited evidence base, to inform recommendations. Several varied species of microorganisms could be found in necrotic bone that may have contributed to inflammation.[37,38] Microscopy, culture and sensitivity-guided antimicrobial therapy is the best practice with empirical broad-spectrum antibiotics reserved to when clinically justified such as in signs of sepsis. [39,40]

Chalem et al[S1] suggested the use of teriparatide for 24 months in the management of MRONJ in patients in the non-cancer setting. Teriparatide is a recombinant fragment of human parathyroid hormone and osteoanabolic agent used for the treatment of osteoporosis. A randomised control trial demonstrated that teriparatide achieved greater resolution for MRONJ and a systematic review identified its use with antibiotic therapy to also be effective.[41,42] Although not mentioned as a recommendation, pentoxifylline and tocopherol with or without clodronate have promising out comes however require further research as current studies have small sample sizes, with short study duration and lack randomisation.[43]

Areas of variability

The implementation of stage. The inclusion of stage 0 shared a moderate consensus. Khan et al[S10] suggested the term could cause overdiagnosis of MRONJ. Conversely, Ruggiero et al[S5] supported the term to identify initial signs of MRONJ for early intervention. One case series reported 51.3% of patients with non-exposure progressed to bone exposure but further studies are required.[44] Yarom et al[S8] modified stage 0 to the term 'increased risk' to highlight the requirement for close monitoring.

Drug suspension for established MRONJ. There is lack of consensus in the guidelines to support suspension of antiresorptive therapy to treat MRONJ. In a retrospective study, the only prognostic observation in improving cases of necrosis was the suspension of bisphosphonates, but the study size was small.[45] There is insufficient evidence to suggest the benefit is greater than the risk to the primary disease thus recommendations should be interpreted cautiously. Drug suspension should be considered on a case-by-case basis and discussion with the prescribing clinician.[S8]

Summary. Managing MRONJ based on diagnostic stage allows for a universal approach. Consideration can be given to surgical intervention as well as conservative management at each stage. An exact protocol for antibiotics has not been established but microscopy, culture and sensitivity should be used to achieve directed therapy early. The use of teriparatide could be considered in non-cancer cases but should be directed by the patient's physician who is managing the osteoporosis.

Evaluation of recommendations against level of evidence. The strength of consensus for recommendations should correlate with the level of evidence (Table 4). For example, there is a high consensus amongst guidelines between recognised risk factors associated with oral health and the antiresorptive therapy, which is based on an intermediate level of evidence. However, some recommendations with a high consensus were based on expert opinion due to lack of evidence such as the indication for antimicrobial prophylaxis prior to invasive dental treatment.[S4]

Limitation of the critical review. The review included sixteen guidelines since the first case of ONJ related to bisphosphonates was reported in 2003.[3] It is a critical review adopting a systematic review methodology and following the PRISMA reporting recommendations, but it lacks interrater reliability scoring. The reviewers selected available guidelines published in English language; hence, foreign language exclusion bias may have been introduced. The focus of the guidelines has been on antiresorptive therapy thus management of other medications, such as angiogenic inhibitors, has not been addressed. This is partly due to the limited evidence of other reported medications causing MRONJ. The AGREE II assessment was undertaken by one author and reviewed by a second author therefore a risk of author bias has been introduced.

Conclusion

1. With the AGREE II tool the review identified four guidelines of high quality.
2. Areas of consensus with intermediate evidence base included risk factors associated with antiresorptive therapy and oral health and prevention strategies prior to initiating therapy.
3. Areas of variability that lacked evidence included patient risk factors, prevention strategies during therapy and treatment strategies for established MRONJ.
4. Further research is required in identifying patient-dependent risk factors, strategies to prevent MRONJ because of invasive treatment and the usage of antimicrobial agents.
5. The review strongly suggests a need for an international collaboration in the creation of MRONJ guidelines.

Table 4
Summary of the consensus of recommendations between guidelines and level of evidence described in the guidelines to formulate the recommendation[S3,S5,S9,S10].

Recommendation	Consensus	Level of Evidence
Risk Factors		
Associated with Antiresorptive Therapy	Strong	Intermediate
Oral Health	Strong	Intermediate
Patient	Moderate	Insufficient to Low
Prevention of Prior to Therapy		
Pretherapy Dental Assessment and Treatment	Strong	Low to Intermediate
Initiation of Therapy after Invasive Treatment	Moderate	Insufficient to Low
Prevention During Therapy		
Regular Dental Examination (3-6 months)	Strong	Low to Intermediate
Promotion of Oral Hygiene and Reduction of Risk Factors	Strong	Insufficient to Low
Antimicrobial Prophylaxis prior to invasive / treatment	Strong	Insufficient
Avoidance of Invasive Treatment	Moderate	Intermediate
Drug Holiday Prior to Invasive Treatment	Moderate	Insufficient
Primary Wound Closure +/- Alveoplasty of Socket	Moderate	Low
Regular Professional Hygiene Appointments	Low	Insufficient
Regular Panoramic Radiographs	Low	Low to Intermediate
Treatment		
Stage-based Approach	Strong	Insufficient to Low
Stage 0	Moderate	Insufficient
Drug Holiday to aide Treatment	Moderate	Insufficient

Conflict of interest

We have no conflicts of interest.

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Ethics statement/confirmation of patient permission

Not required.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjoms.2024.08.008.

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