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Workshop of European Task Force on Medication Related Osteonecrosis of the Jaw. Current challenges

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Complete List of Authors:	Schiødt, Morten; Copenhagen University Hospital, Oral & Maxillofacial Surgery; Aarhus University Hospital, Clinical Epidemiology Otto, Sven; Ludwig-Maximilians-Universitat Munchen, Oral & Maxillofacial Surgery Fedele, Stefano; University College London, UCL Eastman Dental Institute Bedogni, Alberto; Unit of Maxillofacial Surgery, Department of Neuroscience-DNS, University of Padova, Department of Neuroscience-DNS Nicolatou-Gailitis, Ourania; University of Athens, Clinic of Hospital Dentistry Guggenberger, Roman; University of Zurich, Diagnostic and Interventional Radiology Herlofson, Bente; Dental Faculty, Oral Surgery and Oral Medicine; Oslo University Hospital, Unit of Oral and Maxillofacial Surgery, Division for Head, Neck, and Reconstructive Surgery, Department of Otorhinolaryngology Ristow, Oliver; University of Heidelberg, Oral & Maxillofacial Surgery Kofod, Thomas; Copenhagen University Hospital, Oral & Maxillofacial Surgery
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Authors:
Morten Schiodt[1,2], Sven Otto[3], Stefano Fedele[4], Alberto Bedogni[5], Ourania Nicolatis-Galitis[6], Roman Guggenberger[7], Bente Brokstad Herlofson[8,9], Oliver Ristow[10], Thomas Kofod[1].

[1] Copenhagen University Hospital, Department of Oral & Maxillofacial Surgery, Copenhagen, Denmark
[2] Aarhus University Hospital, Department of Clinical Epidemiology, Aarhus, Denmark
[3] Ludwig-Maximilians University Munich, Department of Oral and Maxillofacial Surgery, Münich, Germany
[4] University College London, UCL Eastman Dental Institute and NIHR UCLH Biomedical Research Centre, London, United Kingdom
[5] University of Padova, Department of Neuroscience-DNS, Regional Center for Prevention, Diagnosis and Treatment of Medication and Radiation-related Bone Diseases of the Head and Neck, Padova, Italy
[6] National & Kapodistrian University of Athens, Clinic of Hospital Dentistry, Athens, Greece
[7] University Hospital Zurich, Diagnostic and Interventional Radiology, Zurich, Switzerland
[8] University of Oslo, Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, Oslo, Norway
[9] Oslo University Hospital, Unit of Oral and Maxillofacial Surgery, Division for Head, Neck, and Reconstructive Surgery, Department of Otorhinolaryngology, Oslo, Norway
[10] University of Heidelberg, Department of Oral and Maxillofacial Surgery, Heidelberg, Germany

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Purpose:

This paper reports on the conclusions of two workshops held in Copenhagen in September 2017 and November 2018 focused on medication-related osteonecrosis of the jaws (MRONJ). The workshops were organized and attended by a European task force on MRONJ, i.e. a multidisciplinary group of European clinical investigators with a special interest in the diagnosis and management of MRONJ and a track record of relevant research and publications. The aim of the workshops were to (i) highlight some of the most controversial aspects of current knowledge on MRONJ, including definition and classification, risk factors and management, and (ii) provide an expert opinion-based consensus with a view to inform clinicians and advise researchers, as a first step of reaching solutions.

Introduction:

MRONJ is a potentially serious complication of antiresorptive (AR) treatment in patients with skeletal metastases due to various cancers as well as osteoporosis (Campisi et al., 2014). MRONJ may also develop in antiresorptive-naive individuals exposed to a variety of anti-angiogenic agents (Mohamed, Nielsen, & Schiodt, 2018; Nicolatou-Galitis, Kouri, et al., 2019; Pimolbutr, Porter, & Fedele, 2018). MRONJ may lead to a reduced quality of life due to jaw bone infections, chronic pain, tooth loss, impaired function and disfigurement.

Since the first report by Marx 2003 (Marx, 2003) the number of cases and relevant publications have increased exponentially. Despite significant progress in our knowledge of the disease, there remain a number of controversial aspects that are of high relevance to researchers, clinicians and not least patients. The European task force on MRONJ comprises of a multidisciplinary group of European clinical investigators with a special interest in the diagnosis and management of MRONJ

and a track record of relevant research and publications, who considered the current controversies on MRONJ a reason for academic concern, a potential threat to patients, and a limitation for better research. The Group met up in two separate workshops in order to (i) highlight some of the most controversial aspects of current knowledge on MRONJ and (ii) provide an expert opinion-based consensus on these topics with a view to help clinicians making informed decisions on patient's care and inspire future investigators to design better clinical studies. The Group agreed to focus upon three highly controversial aspects of MRONJ: 1) definition and classification, 2) risk factors, and 3) Management/treatment of MRONJ.

Controversies on definition and classification:

The consensus papers by Ruggiero et al. representing the American Association of Oral and Maxillofacial Surgeons (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws AAOMS, 2007; S. L. Ruggiero et al., 2014; Ruggiero SL;, 2009), have been instrumental in the process of establishing an understanding and acceptance of a widely used definition and classification of MRONJ. The most recent version of the AAOMS consensus (2014) includes (i) the MRONJ case definition as the presence of exposed jaw bone or bone that can be probed through an intraoral or extraoral fistula(e) for at least 8 weeks in a patient receiving antiresorptive and/or antiangiogenic therapy who had not received radiotherapy to the head and neck, and (ii) a disease classification into 4 clinical stages (stage 0-3). The most notable change introduced in the 2014 AAOMS consensus was the modified MRONJ definition so to include patients presenting with an intraoral or extraoral fistula(e). This important amendment was inspired by a number of reports highlighting that a sub-group of patients can in fact present with MRONJ disease characterized by the absence of exposed bone on visual inspection (so called non-exposed MRONJ, including the

presence of an intra-oral fistula, mandibular fracture, dentally unexplained pain and swelling, among other manifestations), and therefore they would not fulfill the case definition of MRONJ as suggested by the initial version of the AAOMS consensus (2007) (Ascani, Campisi, & Junquera Gutierrez, 2014; Bedogni, Fusco, Agrillo, & Campisi, 2012; Fedele et al., 2015; Fedele et al., 2010; S. Patel et al., 2012; M. Schiodt, Reibel, Oturai, & Kofod, 2014; Yarom, Fedele, Lazarovici, & Elad, 2010).

The background was the obviously different interpretations of the term "bone exposure" by different author groups and adjudicators in clinical and epidemiological studies. Some authors regarded bone that can be probed through a fistula as exposed and diagnosed MRONJ in the respective cases while other authors did not include those patients.

The 2009 update of the AAOMS consensus papers (Ruggiero SL;, 2009) partially addressed this issue as they added the new classification stage (stage 0) to include patients presenting with the non-exposed variant of MRONJ. However, the MRONJ case definition remained paradoxically unchanged, therefore preventing non-exposed MRONJ cases to be formally diagnosed, especially in clinical trials and epidemiological studies. (Fedele et al., 2015).

Although the 2014 update of the AAOMS consensus represents a notable improvement, patients presenting with non-exposed MRONJ **without** fistulas (e.g. dentally unexplained pain, mobile teeth not due to periodontitis, numbness of the lip, mandibular fracture) continue to remain excluded from MRONJ case definition (Fedele et al., 2015) (Table 1 and 2). There is therefore an urgent need for expanding the case definition of MRONJ so to encompass the other manifestations of non-exposed MRONJ and ensure that these patients can (i) be formally

diagnosed and treated, and (ii) be included in clinical and epidemiological studies. The Group appreciated that this might be a difficult task as an accurate case definition should ensure the exclusion of etiopathologically different disorders presenting with similar clinical manifestations, which include plaque-related gingivitis/periodontitis, dental and periapical disease, benign fibro-osseous lesion of the jawbones, chronic sclerosing osteomyelitis, infectious osteomyelitis, primary jawbone malignancy, metastatic disease, and TMJ disorders (Fedele et al., 2015; S. Patel et al., 2012; S. L. Ruggiero et al., 2014; M. Schiodt et al., 2014). Excluding these conditions as well as describing the MRONJ lesions requires imaging. The value of imaging is described later under controversies on management/treatment. Some authors have suggested that that up to one quarter of MRONJ patients can present with the non-exposed variant (Fedele et al., 2015). Although this proportion is expected to be somewhat reduced after the inclusion of fistula in the definition (2014 AAOMS paper), efforts should be made to improve and expand case definition so to capture diagnosis in these patients including those with non-exposed MRONJ without fistulas. The Group also suggested that the requirement of 8-week observation of potential MRONJ manifestation to fit the case definition may no longer be necessary. About one third to half of the affected individuals currently develop MRONJ without a history of dental extraction or other trauma (Otto, Pautke, Van den Wyngaert, Niepel, & Schiødt, 2018; Yazdi & Schiodt, 2015) and differential diagnosis with other dental and jawbone disease can be achieved without having to wait for 8 weeks (Bedogni et al., 2012).

Table 1. Staging of MRONJ. After Ruggiero et al. 2014 (S. L. Ruggiero et al., 2014).

MRONJ† Staging
At risk category No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0 No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms
Stage 1 Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection
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
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

† Exposed or probable bone in the maxillofacial region without resolution for greater than 8 weeks in patients treated with an antiresorptive and/or an antiangiogenic agent who have not received radiation therapy to the jaws.

‡ 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.

Table 2:

Mismatch between the 2014 AAOMS case definition criteria (S. L. Ruggiero et al., 2014) and clinical manifestations of MRONJ (modified from Fedele et al. (Fedele et al., 2015).

Clinical Manifestations	Included in the AAOMS definition
Exposed MRONJ	
Frank bone exposure	Yes
Non-exposed MRONJ	
Sinus/fistula tract #	Yes
Bone pain #	No
Bone Swelling #	No
Gingival Swelling #	No
Tooth mobility #	No
Mandibular fracture #	No
Maxillary sinus Pain #	No
Lower lip numbess/dysaesthesia #	No

 # Not caused by dental or other jawbone disease, which should be ruled out with clinical and radiological investigations before suspecting MRONJ diagnosis.

Controversies on risk factors

According to the literature tooth extraction, infection, type and dosage of AR and duration of treatment are considered to be risk factors.

Approximately half to two-thirds of MRONJ cases are reported to develop following a tooth extraction (Otto et al., 2018; Yazdi & Schiodt, 2015). Dental extraction was reported as a main risk factor in 73% of the cases of ONJ (Nicolatou-Galitis et al., 2011), and historically these cases have been identified as a non-healing extraction socket (Bedogni et al., 2012). Accordingly, the vast majority of recommendations on dental treatment of patients on anti-resorptive or anti-angiogenic therapy have included advice against dental extractions as a mean to resolve dental infection (Bedogni et al., 2012; Khan et al., 2008; Khosla et al., 2007; Matsuo et al., 2014; S. L. Ruggiero et al., 2014; Yoneda et al., 2010).

However, a growing body of evidence suggests that dental infection, rather than dental extraction per se, might represent the main local risk factor for MRONJ (Otto et al., 2015; Panya et al., 2017; Saia et al., 2010). For example, a 2011 case-control study with three dental Practice-based Research Networks in US found that the likelihood of developing osteonecrosis was higher (almost double) in patients with a history of suppuration compared to those with a history of dental extractions (OR 11.9 vs 6.6) (Barasch et al., 2011). It is also increasingly reported that dental extractions in patients exposed to antiresorptive therapy usually does not translate into MRONJ development, when tooth extraction is performed using alveolectomy and primary surgical mucosal closure (Heufelder et al., 2014; Otto et al., 2015; Morten Schiodt et al., 2018). Thus, surgical intervention per se should not be over-emphasized as the main risk factor for MRONJ development. Similarly, it has been suggested that infection around the implants (peri-implantitis) represents a notable risk factor for MRONJ development (Giovannacci et al., 2016; Troeltzsch et

al., 2016). This is also in line with the high success rate after surgery on the jawbone to cure MRONJ lesions (see later).

The Group suggested that dental infection might currently be a more common and relevant risk factor for MRONJ compared to extraction, and that a notable proportion of MRONJ cases believed to have been triggered by dental extraction in fact represent cases of non-exposed MRONJ that had already developed because of dental/periodontal infection before the actual extraction took place. Recent studies have reported the presence of histologically-proven alveolar necrotic bone associated with dental/periodontal infection at the time of the extraction of teeth (Nicolatou-Galitis et al., 2015; Nicolatou-Galitis, Schiodt, et al., 2019; Morten Schiodt et al., 2018). Similarly, animal studies have reported that MRONJ can develop to areas of periodontal infection in absence of dental extraction surgery (Nowicki et al., 2019; Otto et al., 2017). Although evidence remains not robust and further well-designed clinical trials are needed, the Group suggested that patients on anti-resorptive therapy should not be declined dental extractions for the treatment of recurrent dental/periodontal infections that cannot be resolved or have failed to resolve with restorative treatment, as the persistence of the infection *per se* represents a notable risk factor for MRONJ development. The group recommended that when needed, tooth extractions should be performed with raising a muco-periosteal flap, alveolectomy, smoothing of bone edges, mobilization of the flap and primary tension free closure of the alveolus with tight suturing.

The Group also highlighted the importance of appropriate stratification of the risk of MRONJ development based on the type, dose and administration route of anti-resorptive medication. There is robust evidence that drug-related factors associated with an increased risk of MRONJ development include nitrogen-containing structure, cumulative high dose, use in cancer setting, and intravenous administration (Abt, 2017; Malden & Lopes, 2012; Otto et al., 2010; S. L. Ruggiero

et al., 2014; Vahtsevanos et al., 2009). However, it should be emphasized that intravenous administration of bisphosphonate per se should not be automatically considered an indicator of the high risk of MRONJ development. For example, some osteoporosis patients receive yearly intravenous bisphosphonates; however, because the cumulative dosage remains low, their risk of developing MRONJ is also low. Furthermore, a low dose, usually quarterly or half yearly , of prophylactic intravenous bisphosphonates has been recently introduced in the management of breast cancer patients without metastases (adjuvant therapy), and this has been reported to be associated with notably lower risk of MRONJ development (V. Patel et al., 2018; Rugani et al., 2014). The Group suggested that, in order to optimize risk assessment and management of patients on anti-resorptive therapy, it is important to highlight to all clinicians, and in particular in the dental setting, that the risk of MRONJ development is mostly associated with high cumulative dosage of nitrogen-containing bisphosphonates. (Fung et al., 2017; S. L. Ruggiero et al., 2014; Yazdi & Schiodt, 2015).

Controversies on management/treatment

Expert opinion-based recommendations for the management of MRONJ are included in the AAOMS position papers (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws AAOMS, 2007; Salvatore L. Ruggiero et al., 2009; S. L. Ruggiero et al., 2014). The Group highlighted that AAOMS treatment recommendations, which are based on a clinically-driven staging system may fail to reflect the actual bone extension of MRONJ disease, with the risk of assigning patients to “inappropriate” treatments (Bedogni et al., 2014).

Accordingly some authors advocated the adoption of treatments based also on the radiological aspects of MRONJ disease (Campisi et al., 2014) in order to pick up early signs of disease or base therapeutic decisions on accurate assessment of disease extent. However, there remains no consensus on the efficacy of different radiological imaging modalities (e.g. CT, MRI or nuclear imaging) in assessing, with high accuracy, the "true" MRONJ disease extent. (Bisdas et al., 2008; Devlin et al., 2018). A number of studies have compared specific imaging modalities and found inconsistent results in terms of overestimation/underestimation of the extension of MRONJ (Guggenberger et al., 2013; Stockmann et al., 2010).

The Group advised that clinicians should be careful in adopting treatment recommendations that are solely based on clinical assessment of MRONJ patients, and that further imaging studies are needed in order to study the extension of necrotic bone disease in MRONJ patients.

The Group also highlighted the current controversy on surgical management of MRONJ patients. The AAOMS recommendations suggest generally non-surgical treatment for stage 1 and 2, and performing surgical debridement/resection of necrotic bone only for Stage 3 MRONJ patients (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws AAOMS, 2007; Salvatore L. Ruggiero et al., 2009; S. L. Ruggiero et al., 2014).

However, there is an increasing body of evidence suggesting that surgical removal of necrotic bone might be curative in patients with all MRONJ stages (Aljohani et al., 2019; Otto et al., 2018; Ristow et al., 2018; Morten Schiodt, Ottesen, Dalsten, Oturai, & Kofod, 2016), where cure is defined as long-term resolution of symptoms and complete mucosal closure (absence of residual bone exposure). For example, Schiodt et al. reported resolution of symptoms and complete mucosal closure in 93% of 141 MRONJ patients treated with surgical removal of necrotic bone as

compared to only 17% of 63 non-surgically treated cases (Morten Schiodt et al., 2016). Other studies have documented high success rate of surgical treatment compared to non-surgical treatment (Aljohani et al., 2019; Hauer et al., 2019; Yamada et al., 2018).

A recent study also suggests that non-surgical therapy might lead to progression of MRONJ disease. Ristow et al. (2019) described a longitudinal study of 92 patients with stage 1 MRONJ who were initially treated by using a standardized conservative (non-surgical) protocol consisting of antimicrobial mouth rinsing and gel application (with chlorhexidine). The authors reported that only 8 patients (8.7%) showed complete mucosal healing and resolutions of symptoms whereas the remaining 84 (91.3%) had persistent exposed jaw bone at end of the observation period (15.6 months). Among these 84 patients, 67 (80%) showed progression of their MRONJ disease (upshift in AAOMS stage from 1 to 2 or 3), which eventually led to extensive bone and/or tooth loss in 28 cases (Ristow et al., 2019). The Group highlighted that, although well-designed comparative trials are required, there is increasing evidence suggesting that surgical removal of the necrotic bone might provide long-lasting benefits to MRONJ patients in terms of resolving symptoms, obtaining mucosal healing, and preventing further progression of necrotic bone disease. With this growing body of evidence, a number of clinicians have shifted their therapeutic approach from conservative (non-surgical) to upfront surgical treatment.

Recommendations

Based on the discussion points summarized above, the Group has produced a number of consensus key statements and recommendations so to inform clinicians and advice researchers, as a first step of reaching solutions.

Key statements and recommendations relevant to definition and classifications of MRONJ:

- Current widely adopted definition does not identify all patients affected by MRONJ
- The current description of stage 0 is controversial, does not fulfill the definition of the disease and may be misleading and difficult to interpret.
- Stage 0 of the AAOMS classification is a diagnostic challenge, as there are overlaps with dental and non-dental diseases. Stage 0 may ultimately need confirmation by imaging and/or histopathology.
- Cases of non-exposed MRONJ without fistula should be included in the definition, possibly in terms of suspected or probable MRONJ after ruling out other dental and non-dental disease. The only ultimate proof of non-exposed MRONJ might be the histopathologic confirmation of necrotic bone. Decision on biopsy should be taken on an individual basis.
- The definition criterion of 8 weeks bone exposure/probing of bone does not apply to all cases and may delay diagnosis and consequently treatment.
- The role of imaging in the definition and classification of MRONJ needs further refinement. Imaging may aid in diagnosis (especially for non-exposed cases) and help determining disease extension and planning treatment.
- Present classification/staging does not adequately capture the extension and severity of MRONJ lesions. This may potentially affect treatment and prognosis.

Key statements and recommendations relevant to risk factors for MRONJ:

- Tooth extraction does not automatically translate into an increased risk of developing MRONJ, as certain surgical procedures notably reduce the risk.

- The reported high risk of developing MRONJ after tooth extraction might be related to an underlying pre-existing dental/periodontal infection rather than to the surgery *per se*.
- The risk of developing MRONJ is not related to the way of administration as single factor; an accurate risk assessment should include an evaluation of the cumulative dosage and duration of anti-resorptive treatment. Typically, high dose anti-resorptive therapy given to cancer patients with metastases is associated with higher risk of MRONJ development as compared to low dose therapy given to osteoporosis patients.

Key statements and recommendations relevant to management/treatment of MRONJ:

- Because there is no accurate staging system reflecting the extension of MRONJ bone disease, it is problematic, and possibly misleading, to inform treatment recommendations on the basis of currently available staging systems.
- The term “conservative treatment” is used inconsistently in the literature and might include a number of different interventions ranging from topical antimicrobial mouthwashes to removal of superficial loose sequestra.
- The Group recommends using the terms non-surgical vs. surgical treatment.
- Recent literature suggests that non-surgical treatment may lead to disease progression.
- Surgical treatment is superior to non-surgical management in promoting long-term mucosal healing as well as absence of symptoms or radiologic signs indicative of bone necrosis.
- If the aim of treatment is reduction of symptoms (pain) and control of infection, non-surgical treatment may be a valid management option. This seems particularly appropriate in frail elderly patients and in end-of-life oncology palliative setting.

- Early surgical intervention on localized disease may prevent progression and the need for subsequent extensive surgery (consider to treat surgically and early).

GENERAL SUMMARY

The Group has highlighted a number of controversial aspects of current knowledge and practice relevant to MRONJ, which have the potential to affect clinical management of patients as well as research. The Groups suggest that key statement and recommendations presented in this paper might represent a useful tool so to stimulate a proactive discussion and inspire new and better-designed research, as first step to reach a consensus and improve the management of patients with MRONJ.

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