# Where is the Evidence? The role of Microbiology in the Treatment of Medication Related Osteonecrosis of the Jaw (MRONJ)

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## Introduction

Since the first reported case in 2002, many case series and acronyms describing osteonecrosis of the jaw (ONJ) have been published[1]. MRONJ, a form of avascular necrosis initially associated with bisphosphonates, has more recently been recognised as a complication of the receptor activator of nuclear factor kappa B (RANK) ligand inhibitor denosumab and the antiangiogenic agent bevacizumab[3]. This association with other agents prompted the updated definition of MRONJ by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014[1].

**The AAOMS criteria for diagnosing MRONJ is as follows:**

- **Current or previous treatment with antiresorptive or antiangiogenic agents;**
- **Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks; and**
- **No history of radiation therapy to, or obvious metastatic disease in the jawbones.**

Despite the first cases of ONJ being reported over a decade ago, the pathophysiology of MRONJ is still not fully understood. Many hypotheses to explain the localisation of necrosis to the mandible and maxilla have been proposed including over suppression of bone resorption and bone remodeling, inhibition of angiogenesis and microtrauma[1-4]. Infection and inflammation have also been postulated as playing an important role in disease. Complex biofilms composed of Actinomyces and other organisms have been identified on bone and mucosal surfaces in MRONJ. Whether this represents primary or secondary infection is unknown.

Guidelines from the American Society of Clinical Oncology (ASCO), the AAOMS and the European Medicines Agency (EMA) all recommend the use of antimicrobial therapy as part of the management of MRONJ even with the paucity of high quality clinical trails. To date there is no evidence-based guidance on which to base recommendations. Furthermore there are few publications describing the microbiological investigation of MRONJ or the epidemiology of disease. Data on antimicrobial resistance is also lacking.

## Aims

Our aim was to review the available literature focusing on the microbiological aspects of MRONJ disease and its management. The objective was to evaluate guidance recommendations on appropriate sampling and microbiological investigation, antimicrobial therapy (agent and duration) and outcome measures used to establish response to treatment.

**Table 1** Summary of microbiological investigation and antimicrobial management of MRONJ[1-29]
NS, Not specified; NA, Not applicable

| Study | Design (No. of patients) | Microbiological investigation & Causative pathogen (s) | Antimicrobial therapy | Duration |
|---|---|---|---|---|
| **Bedgoni *et al*** **2011** | Cohort Study (n=30) | NS | Sulbactam/Amoxicillin + Metronidazole or Lincomycin | 10 days |
| **Chiu *et al*** **2010** | Case Series (n=12) | NS | Penicillin or Levofloxacin; with Chlorhexidine | 14 days or until pain subsides |
| **Ferlito *et al*** **2012** | Observational Study (n=91) | NS | Chlorhexidine or Povidone +/- Piperacillin-tazobactam or Imipenem | 2 days pre op followed by 3 days post seqeustrectomy |
| **Freiberger *et al*** **2012** | Randomised Controlled Trial (n=46) | NS | NS | NA |
| **Hoefert *et al*** **2011** | Retrospective review (n=46) | NS<br>No positive cultures for *Actinomyces spp* | Beta-lactam or Clindamycin or Fluoroquinolone or Doxycycline; with Gentamicin rinses | Short-term therapy: 3-10 days (median)<br>Long-term therapy: 4 weeks pre-op followed by 1-2 weeks post-op |
| **Junquera *et al*** **2009** | Retrospective review (n=21) | Biopsy/sequestrum sampling<br>*Actinomyces spp; Eikenella spp; alpha-haemolytic streptococci* isolated | NS | NA |
| **Lazarovici *et al*** **2009** | Case series (n=101) | NS | Mild ONJ: Amoxicillin or Doxycycline or Clindamycin<br>Severe ONJ: Penicillin or Clindamycin | 4-6 weeks, prolonged therapy not specified extended beyond clinical resolution |
| **Markose *et al*** **2009** | Case series/ Protocol (n=15) | NS | Clindamycin<br>Chlorhexidine mouthwash | NS |
| **Mawardi *et al*** **2009** | Case Series (n=5) | NS | Amoxicillin or Co-amoxiclav or Clindamycin; with Chlorhexidine | 2-12 weeks |
| **Moretti *et al*** **2011** | Cohort (n=34) | NS | Co-amoxiclav or Ciprofloxacin; with Metronidazole | 10 days |
| **Mücke *et al*** **2010** | Prospective cohort (n=108) | NS<br>*Actinomyces spp* isolated | Clindamycin or Co-amoxiclav or Penicillin | NS |
| **Nicolatou-Galitis *et al*** **2011** | Prospective case series (n=162) | NS | Amoxicillin +/- Metronidazole or Co-amoxiclav followed by Amoxicillin or Clarithromycin + Metronidazole or Clindamycin | 2 weeks or until symptoms subsided |
| **Rasmussen *et al*** **2014** | Review Article (NS) | NS | Flucloxacillin or Clindamycin | NS |
| **Stockmann *et al*** **2009** | Prospective case series (n=50) | Bone smear (Not specified further)<br>*Actinomyces spp* isolated | Amoxicillin or Clindamycin | NS |
| **Scoletta *et al*** **2010** | Prospective review (n=37) | NS<br>*Actinomyces spp isolated* | Co-amoxiclav or Clindamycin | 7 days |
| **Vescovi *et al*** **2011** | Case Series (n=151) | NS | Amoxicillin or Metronidazole Chlorhexidine | 2 weeks |
| **Williamson *et al*** **2010** | Prospective Case Series (n=40) | NS | Pre and post-op Amoxicillin or Clindamycin | Minimum 2 weeks post-op |
| **Yarom *et al*** **2006** | Retrospective review (NS) | Resected bone/superficial seqeustrectomy samples<br>Mixed microorganisms including *streptococci* isolated | Amoxicillin or Doxycycline | Long term therapy Not specified further |

## Method

A literature review was performed using the following databases; OVID (Medline, Embase), EBSCO collections (CINAHL), Cohrane Library, Pub Med (the US National Library of Medicine) and Google Scholar. The key words used for this search included Bisphosphonate related Osteonecrosis of the jaw (BRONJ), Medication related Osteonecrosis of the jaw, infection, microbiology, conservative management, and antimicrobial therapy.
The last date of the literature search was 20th December, 2014. Only articles in English were included in this review. The initial search identified 113 articles of which 18 articles were included in this review.

## Results

A comprehensive evaluation demonstrated important discrepancies in MRONJ management and re-enforced need for further high quality studies.

No consensus opinion or guidance on microbiological investigation could be drawn from the studies. Specifically there was a lack of detailed information on types of culture media, incubation period or atmospheric conditions used. Additionally there was very little information published on species identification or susceptibility testing performed.

Most studies provided limited epidemiological information. *Actinomyces spp.* was reported by many studies as the most consistently isolated organism, but information on whether Actinomyces was deemed a pathogen or coloniser was lacking.

In terms of antimicrobial therapy, there was vast variation in the agent(s), route and duration of therapy used. Follow-up periods and outcome measures used to establish response to treatment were also poorly defined.

A summary of microbiological investigation and antimicrobial management of MRONJ for each study reviewed is listed in Table 1.

## Conclusions

The role of infection in the progression and pathogenesis of MRONJ remains unclear, leading to the validity of any given antimicrobial therapy regime being debated.

More robust studies are required to better understand the role of infection in this disease. Additionally studies must expand upon microbiological investigation and antimicrobial management in order to guide future therapeutic interventions and generate a standard practice to which further studies can be compared.

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