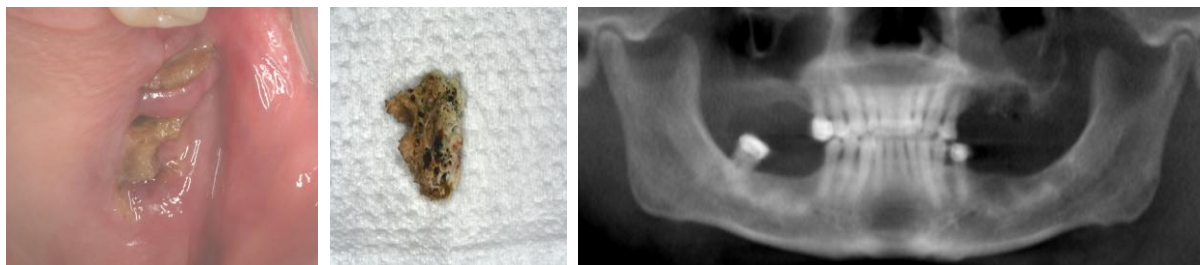


## Osteonecrosis of the jaw secondary to bisphosphonate therapy: Background, clinical features, pathogenesis, therapeutic rationale and protocols

### Background

Osteonecrosis of the jaws (ONJ) secondary to bisphosphonate (BP) therapy is an emerging health problem that may be associated with significant morbidity such as oral dysfunction, impaired eating ability, pain and compromised esthetics, resulting in poor quality of life in affected patients. The BPs are a class of pharmaceuticals that have anti-resorptive, anti-angiogenic and anti-neoplastic properties; they are predominantly used in the treatment of numerous disorders that affect *bone*, including osteoporosis, cancer metastases to bone, hypercalcemia of malignancy, and multiple myeloma. Currently, the pathogenesis of ONJ is poorly understood and clinical and epidemiologic studies are lacking, therefore no evidence-based therapeutic protocols exist for treating the condition. Diagnostic criteria are not well-established, inclusion and exclusion criteria in reported cases are lacking, animal models are just being established, and no prospective studies have been conducted to characterize disease process or identify early-stage disease. Preventive dentistry has been recommended as the only measure for trying to prevent disease, but this is not always successful nor is the outcome predictable for every patient. *Significant research into ONJ is necessary, at both the basic science and clinical level, in order to elucidate the pathogenesis and provide insight and rationale for therapeutics.*

Importantly, in the **clinical course** of ONJ, exposed and necrotic bony *sequestra* often appear as shown in **Figure 1** below and may be the hallmark of disease:



**Figure 1.** One of our clinical patients with ONJ is shown here with bony sequestrum protruding through the ulcerated alveolar mucosa (left). The patient was given intravenous N-BP for several months for metastatic prostate cancer, and this site of involvement is where previous dental extractions were performed. In the middle is the gross specimen of dead bone from the same patient following spontaneous sequestration a few weeks after initial presentation, and to the right is a panoramic reconstruction from a cone-beam CT scan of his jaws.<sup>1</sup>

**Table 1.** Clinical staging of ONJ (Adapted from Ruggiero *et al*, OOOOE, 2006)

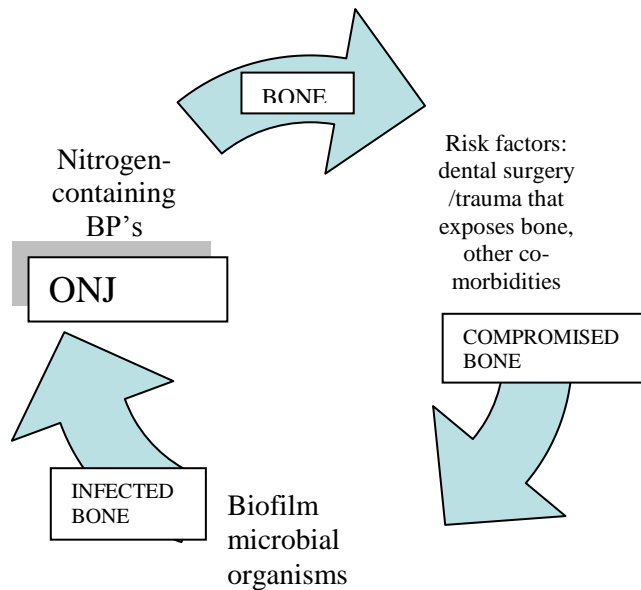
The importance of sequestration in the disease process is reflected in the clinical staging system for ONJ as shown in **Table 1** to the right. The necrotic bony sequestra seen in ONJ are similar to that seen in *osteomyelitis* of the jaw, which is an infection of the jaw bones usually caused by oral flora. Further, treatment or control of ONJ may ultimately require surgical

Stage 1	Exposed, necrotic bone (sequestra) that is asymptomatic
Stage 2	Exposed, necrotic bone (sequestra) associated with pain and infection
Stage 3	Exposed, necrotic bone (sequestra) in patients with pain, infection and pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border of the mandible or the maxillary sinus

debridement of affected bone, or sequestrectomy similar to that performed for osteomyelitis of the jaw. Antibiotic therapy, including local antimicrobial mouth rinses and/or systemic treatment depending on extent of disease, has been recommended to control ONJ (similar to osteomyelitis of the jaw).<sup>ii</sup> Interestingly, prior to BPs being implicated in the etiology of ONJ, cases of ONJ were diagnosed as osteomyelitis of the jaw using histopathologic and radiographic criteria.<sup>iii</sup> The reason for this is that although ONJ and osteomyelitis of the jaw have different etiologies, they share similar clinico-pathologic features. This is especially true when *sequestration* occurs, because at this point the clinical distinction between the two conditions may be arbitrary for the clinician who is ultimately dealing with necrotic and exposed bone regardless of the etiology or nomenclature.

To address difficulties in treating bone infections, Orthopedic Surgeons have recently adopted **biofilm theory** to explain the **pathogenesis** and to guide the management of long bone infections.<sup>iv</sup> A biofilm is a microbially derived sessile (bound) community, as compared to planktonic (free-floating) organisms. Biofilms are characterized by a community of cells that are attached to a surface, are embedded in a matrix of extracellular polymeric substances that they have produced to connect to and communicate with each other, and exhibit an altered phenotype with respect to growth rate, gene transcription and antimicrobial resistance.<sup>v</sup> Biofilm theory has emerged to explain the etiology of the infections that have come to constitute between 65-80% of the microbial diseases treated by physicians in the developed world.<sup>vi</sup> In long bone osteomyelitis the causative microbes, which in most cases are *staphylococci*, have been shown to grow as bacterial biofilms on the bone surface and are notably resistant to antibiotics and host defenses as compared to their planktonic counterparts.<sup>vii,viii</sup> Further, laboratory diagnosis and clinical management of infectious disease is predicated on the identification and treatment of *planktonic* bacteria, which is inappropriate for the evaluation or treatment of *biofilms*, or what are commonly referred to as unculturable bacteria.<sup>ix</sup>

Our research laboratory recently characterized ONJ as a biofilm-mediated disease involving oral pathogenic flora.<sup>x</sup> Every clinical ONJ patient with sequestering and necrotic bone we have encountered has evidence of biofilm organisms when their tissue is examined with biofilm-applicable methodologies as compared to routine culturing techniques. These organisms include bacteria and fungus, often found co-aggregation is seen among different species. These findings help explain why this complication only affects the jaw bones even though BP's are distributed to all bones in the body, because these are the only bones regularly exposed to bacteria after certain dental procedures.<sup>xi</sup> Therefore, the clinical problem is a biofilm infection of bone secondary to bone exposure, and the BP drugs contribute to this pathogenesis by changing the stereoelectronic properties of the bone surface where they localize, making it a favorable environment for microbial colonization and growth. Therefore, our protocol for disease prevention and treatment is predicated on knowledge of the biofilm mode of pathogenesis in the context of bisphosphonate etiology in susceptible patients. The most susceptible patients, or at-risk patients, are those with: 1) a previous history of ONJ, 2) patients with co-morbid conditions that may affect wound healing or blood supply (e.g. diabetes, radiation therapy, chemotherapy, and hypertension), and 3) those undergoing dental procedures or having ill-fitting dental prostheses that may expose jaw bone to significant microbial colonization (e.g. tooth extraction or denture trauma). These factors as shown below in the schematic are all important to understanding the etiopathogenesis and ultimately treatment of ONJ.



### Protocols

It is important to note that the benefits of this class of drug usually far outweigh the risks, and since these drugs have long half-lives lasting many years in bone, discontinuation or a drug holiday may not be beneficial or even possible in many cases. Therefore, patients should not discontinue taking these drugs and should always consult their physician for any information pertaining to their therapy and prescription. Importantly, ONJ is a preventable and manageable condition.

As summarized in **Table 2** below, if a patient is going to be placed on a nitrogen-containing BP by their physician or is on one already, a dental consultation or evaluation is appropriate for establishing good oral hygiene and treating any odontogenic and periodontal pathology before longer term drug use is realized. ONJ appears to be a time and dose-dependent phenomenon, so the longer patients take the medications the greater the risk for ONJ. Periodontal therapy (e.g. scaling and root planing) and maintenance is warranted to favor a healthier oral microbial environment, and fabrication or adjustment of dentures or dental prostheses is also warranted to ensure no ill-fitting prostheses exist that can result in mucosal ulceration and potential jaw bone exposure. Any necessary tooth extractions or oral surgical procedures affecting bone should be done before starting BP therapy or early during therapy.

If a patient is taking a BP already, and requires a dental procedure such as a tooth extraction that may be associated with jaw bone exposure to the oral cavity and saliva (where biofilm organisms reside), we recommend that if an evaluation and risk assessment deems it appropriate, to place the patient on a 1 week pre-operative irrigation (mouthrinsing) regimen of liquid chlorhexidine gluconate 0.12% and nystatin (3x/day), an immediate pre-op mouthrinse of the same, and continuation of the mouthrinsing 1 week post-op or until complete healing has occurred with no evidence of bone exposure or sequestration. These are rinse and spit regimens, no swallowing or systemic absorption is needed and generic or brand name doesn't matter. Nystatin is often not necessary in the regimen unless healing doesn't occur after months of treatment. Chlorhexidine may stain teeth and oral structures and patients should be informed of this prior to use. No drug is without side-effects, including the ones used here, and patients should be made aware of this prior to use as with all medications. Contraindications and drug interactions should also be considered. In general, these

patients also require more diligent and routine follow-up as compared to healthy patients that are not at risk for ONJ.

If a patient has an active localized lesion of ONJ without significant spread or bacteremia, the treatment protocol initially involves irrigation 3x/day with chlorhexidine and nystatin rinses until the lesion resolves. Monoject syringes may be needed in some cases to get the fluids to the bone when sinus tracts are present or mucosal openings to the bone are small and the bone is less accessible for irrigation through gross mouthrinsing. Some clinicians use hydrogen peroxide, saline water, dilute bleach or iodine-based medicaments in addition to other agents for such irrigation techniques, however, no studies exist yet testing the efficacy of any treatment agent, including chlorhexidine and nystatin. The key is wound management regardless of the agent used, and more caustic agents should be avoided around vital anatomic structures such as nerves. Early cases of ONJ often require conservative treatment while more advanced cases may require more invasive procedures. The key to clinical success is patient compliance with home care regimens, so communicating with the patient or caretaker clearly and specifically regarding treatment aims and goals is necessary for success. Ultimately, patients should be managed according to their presentation, which may include rinses for weeks to months until mucosal healing occurs and bone is completely covered by mucosa with no sinus tracts, possibly oral antibiotic use (Clindamycin, Amoxicillin, Azithromycin or Metronidazole) for weeks at a time, and/or gentle debridement and irrigation. Soft acrylic stent fabrication may be needed when exposed or sharp bone causes trauma to adjacent soft tissues such as the tongue or other oral structures. In advanced cases with symptoms such as paresthesia, dysesthesia, anesthesia or pain, sequestrectomies and other bone surgeries may be performed as needed to control disease or prevent further progression. Septicemia is rare in this setting though a possibility and should be managed accordingly and as emergent situation with IV antibiotics, culture and sensitivity testing. Oral Surgery consultation is recommended in most cases for management, especially for advanced cases. Imaging studies can also play an important role in screening, diagnosis and follow-up in many cases. Commonly used modalities include panoramic radiography, CT and cone-beam CT. There are also studies assessing serum bone markers (e.g. serum CTX)<sup>xii</sup> prior to procedures, but their validity and reliability remains unproven and there is a cost associated with their use.

For the best interest of each patient, clinical decision-making, pharmacotherapeutic decisions, and risk assessment for ONJ should occur on a case-by-case basis ideally with all treating doctors involved, and taking into consideration all known factors in order to ensure complete disclosure, accurate treatment planning, and obtaining truly informed consent for any therapeutics or lack thereof.

**Table 2.** Summary of prevention and treatment protocols

<b>Pre-BP patient</b>	Dental evaluation and establishment of good oral hygiene, risk assessment	Treatment of any odontogenic and periodontal pathology
<b>BP patient undergoing dental surgery</b>	Risk assessment, 1 week pre-op and 1 week post-op antimicrobial rinse	Immediate pre-procedure rinse
<b>BP patient with active ONJ</b>	<i>Early stage:</i> antimicrobial irrigation 3x/day or after meals until the lesion resolves with regular f/u and debridement prn	<i>Advanced stage:</i> surgical therapy and/or antibiotics (oral or IV prn)

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