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Update on Medication Related Osteonecrosis of the Jaw

A Peer-Reviewed Publication
Written by Frieda Atherton Pickett, RDH, MS

Abstract
The American Association of Oral and Maxillofacial Surgeons recently updated management recommendations and related information for osteonecrosis of the jaw. The condition formerly referred to as bisphosphonate-related osteonecrosis of the jaw (BRONJ) was renamed medication-related osteonecrosis of the jaw (MRONJ) due to reports of several non-bisphosphonate drugs resulting in the loss of alveolar bone and clinically appearing similar to BRONJ. This course will cover new information on proposed etiologies, mechanisms of drug actions and physical events which may be related to development of the loss of alveolar bone. All pharmacologic agents proposed to play a role in the development of the alveolar bone destruction will be identified and the degree of risk for each agent discussed. Information to discuss with patients taking medications associated with MRONJ is included to assist in patient information identified in the AAOMS guidelines.

Educational Objectives
At the conclusion of this educational activity participants will be able to:

1. Define the terms used to describe osteonecrosis of the jaw (ONJ) associated with various drugs.
2. Explain the factors that can lead to development of medication related ONJ (MRONJ).
3. List the various medications implicated in ONJ and their mechanisms of action.
4. Describe prevention measures and management strategies when drugs associated with ONJ are reported on the health history.

Author Profile
Frieda Atherton Pickett, RDH, MS, graduated from the Masters of Science, Dental Hygiene Education program at the University of Missouri-Kansas City in 1970 and has taught in, directed programs for and authored texts and courses for the dental hygiene profession over the past 45 years. Frieda has received many awards and lectures internationally. Ms. Pickett has served as a test constructor for the American Dental Association Dental Hygiene National Board Committee. She continues to investigate new products and methods to deliver oral services and currently serves on the Access to Care Committee for the Tennessee Dental Hygienists’ Association. Frieda can be reached at fpickett2@gmail.com.

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Introduction
In the mid-1990s reports began to appear in the professional literature of implant failures and osseous destruction affecting both the mandible and maxilla in individuals who took an oral form of a bisphosphonate classification of drug. At first, all case reports involved alendronate (Fosamax®), a drug used to ameliorate the effects of osteoporosis by reducing the physiologic resorption of bone (i.e. an antiresorptive effect). Later reports revealed that bisphosphonate drugs administered by intravenous (IV) pathway, principally during cancer chemotherapy, were associated with similar osseous destruction in the jaw. The lesion of the jaws resembled a condition reported in the 1800s, referred to as “phossy jaw”, occurring in industrial workers in match factories. The workers used a paintbrush to place a phosphorous dot onto the ends of the matchstick, which would then light when struck. Workers shaped the brush tip into a point with the lips before the dots were added to the matchstick. Phosphorous was theorized to be a major factor in the development of the bony destruction. This led to the theory by practitioners in the 1990s that some component of the bisphosphonate chemical structure caused the jaw pathology. Since the bone destruction was a new adverse effect, there was little reliable research on the condition. Due to case reports indicating that all patients had taken alendronate (Fosamax®), the widely prescribed bisphosphonate drug was identified as a potential cause of the bone destruction. Professional organizations began to develop an evidence base to identify causation, prevention and best practices for treatment. The condition was referred to by a variety of names, such as bisphosphonate osteonecrosis of the jaw (BON) or bisphosphonate related osteonecrosis of the jaw (BRONJ). Most cases developed following several years bisphosphonate usage.

New medications, unrelated to the bisphosphonate class, were developed for the treatment of osteoporosis by inhibiting osteoclast function. Denosumab, a human monoclonal antibody, was introduced in the 2000s. There are two indications for these drugs; to prevent bone loss in metastatic disease (Xgeva®) and to prevent bone loss in osteoporosis (Prolia®). Osteonecrosis of the jaw began to be observed in individuals who took denosumab, leading the American Dental Association, Council on Scientific Affairs, Expert Committee on Antiresorptive Agents, to update management considerations and propose new nomenclature, referring to the condition as “antiresorptive agent-induced osteonecrosis of the jaw” (ARONJ).

Recently antiangiogenic agents used in cancer chemotherapy (sunitinib [Sutent®] and bevacizumab [Avastin®]) received an advisory warning from the Food and Drug Administration (FDA) regarding the potential development of ONJ. Antiangiogenic agents reduce blood vessel formation within tumors. In response to the expanding list of medications associated with ONJ, the American Association of Oral and Maxillofacial Surgeons (AAOMS) updated their position statement in 2014 and proposed renaming the condition “medication-related osteonecrosis of the jaw” (MRONJ). The 2014 update: (1) includes information on the differential diagnosis for the condition, (2) defines stages of the condition, and (3) provides evidence-based prevention measures and dental management strategies for individuals with MRONJ.

CASE REPORT
A 61 year old male presented to his general dental office complaining of pain in his jaw and areas of exposed bone. A history of the condition is described as follows:
January 2004: The subject developed an orbital inflammatory condition of unspecified etiology, for which he sought medical care at the University of Texas Southwestern Medical Center at Dallas. The neuro-ophthalmologist managing the orbital condition prescribed prednisone to reduce the inflammatory effects of the condition. Since it was known that a potential side effect of this anti-inflammatory agent was bone loss/osteoporosis, the physician prescribed concurrent administration of a daily dose of bisphosphonate, 10 mg alendronate (Fosamax®).
Onset of Oral Symptoms
The first symptom of osteonecrosis of the jaw was noticed six months later, and the chief complaint was “pain in the jaw”. The patient was leaving for a two week vacation and did not seek treatment immediately. During the vacation the pain increased. When he returned home, he contacted the neuro-ophthalmologist, as he suspected the symptom may be related to the inflammatory condition or the associated pharmacologic therapy. The oral examination by the physician revealed multiple lesions, similar to ulcerations. Behcet’s syndrome was suspected due to multiple large ulcerations in the floor of the mouth, buccal mucosa and the throat. Later testing eliminated Behcet’s syndrome as the cause. Soon thereafter, an exudative lesion, similar to a sinus tract, developed on the chin. Further examination revealed a loss of epithelial covering of the labial anterior mandibular mucosa and lingual mucosa of the posterior right jaw, with exposed bone along mandibular tori (Figure 1). The subject was referred to an infectious disease (ID) specialist by the ophthalmologist.

In September 2004 the OS examined the oral ulcerations and the exposed bone. The OS decided not to remove the large ulcerations and the patient scheduled an appointment to see a plastic surgeon who surgically excised four ulcerations and biopsied the tissue, with a preliminary diagnosis of squamous cell carcinoma. Histology ruled out malignancy and verified the presence of an inflammatory ulcerative condition. At this time little was known about BRONJ by dental and medical practitioners.

The subject was a pharmacist with many years of experience. He recalled reading articles describing the possible side effect of exposed bone in the jaw from taking a bisphosphonate drug, specifically IV administered zolendronic acid (Zometa®) and the oral dose form, alendronate. Many reports speculated the condition was associated with immunosuppression. The subject wondered if the prednisone, along with the bisphosphonate (Fosamax®), had put him at risk for ONJ. At a subsequent visit to the OS a diagnosis of BRONJ was made and the areas surrounding the necrotic bone were debrided to promote healing.

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The patient decided to see his general dentist, who took intraoral photographs of the lesions (Figure 2) and referred the patient to an oral surgeon (OS). Prior to seeing the OS, the subject presented to the ID specialist for culture and sensitivity testing (CST). Based on results of the CST, Augmentin®, 500 mg tid, was prescribed. The antibiotic was taken from August to December 2004.

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Resolution of Symptoms
One year later symptoms exacerbated. The OS debrided the exposed bone and appointed the subject for further examination and subsequent debridement of the area. A culture was ordered for debris from the debrided area, and a diagnosis of “actinomycosis” was made. Actinomycosis is a bacterial infection caused by Actinomyces israelii, an uncommon infection in the mouth. A venous access port was placed at the clavicle to administer medication and the subject was given an IV administered antibiotic, Invanz® (ertapenem), an antibiotic used to treat moderate to severe infections (abdominal, skin, lung, or other organ systems) caused by bacteria susceptible to the drug. The patient received Invanz®, 1 gram, IV daily for six weeks. The lesions improved and less pain was noticed. The patient was again placed on Augmentin® 500 mg tid until April, 2005 and subsequently dismissed from care. Since bisphosphonate can remain within the bone for many years, future sequestra may develop.

Over a period of six years the lesions re-epithelialized. In 2011 a bony sequestrum was noticed by the patient on the lingual aspect of the right mandible and a return visit to the OS was made. The OS removed the bone spicule and the gingival tissue healed. The incident was accompanied by little to no pain, but was irritating to the tongue. At the present time (two years later, April 2013) no oral lesions have returned, nor bony sequestra (Figure 3), but significant bone loss is evident (Figure 4). Recently, due to the extreme loss of bone and difficulty in cleaning the area, periodontal problems have developed.
The early reports of BRONJ identified several cases where drugs that reduce host immune response to inflammation (such as prednisone) were taken. Infections with *Actinomyces israelii* microorganisms in the affected area were sometimes reported and antibacterial agents were prescribed. Antibacterial mouthrinses, such as chlorhexidine, were recommended in the past, as well as debridement of necrotic tissue and removal of sequestra. According to the 2014 AAOMS position paper, a person may be judged to have MRONJ if all of the following properties are present:

1. Current or previous treatment with antiresorptive or antiangiogenic agents.
2. Exposed bone or bone that can be probed through an intraoral or extraoral sinus tract in the maxillofacial region that has persisted for more than eight weeks.
3. No history of radiation therapy to the jaws or obvious metastatic disease of the jaws.

The AAOMS paper further noted that; “ONJ uncommonly occurs in patients not exposed to antiresorptive or antiangiogenic agents.”

Reducing blood supply in tumors (to reduce growth of cellular elements) is important in cancer chemotherapy. Antiangiogenic agents also reduce tumor invasion of blood vessels, thereby reducing metastasis. ONJ has been referred to as “avascular necrosis” indicating an antiangiogenic effect. This is one of the proposed etiologic factors in the development of ONJ. Antiangiogenesis is associated with zolendronic acid and other IV administered cancer chemotherapy drugs, such as sunitinib (Sutent®) and bevacizumab (Avastin®).

### Implications For Management Of Patients

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The AAOMS paper further noted that; “ONJ uncommonly occurs in patients not exposed to antiresorptive or antiangiogenic agents.” Although much research has been completed to clarify the condition, the pathophysiology is still not fully understood. The AAOMS paper notes that debate is ongoing regarding the mechanism for ONJ from these drugs. Proposed hypotheses include “altered bone remodeling or oversuppression of bone resorption, angiogenesis inhibition, constant micro-trauma, suppression of innate or acquired immunity, vitamin D deficiency, soft tissue toxicity from bisphosphonates, and inflammation or infection.”

Antiresorptive agents, such as bisphosphonates or denosumab, inhibit differentiation of osteoclasts, and increase apoptosis (cellular death) of osteoclasts which lowers physiologic resorption of bone. This process is helpful in skeletal sites, but osteonecrosis in the alveolar bone of the jaw is possible. Tables 1 and 2 summarize dental management recommendations for patients expecting to initiate treatment with antiresorptive therapy, or those already taking the drug, and for patients with cancer who must receive the drugs by IV administration.

### Predisposing Risk Factors

Dental infection has been implicated as a factor in MRONJ since tooth extraction appeared to result in ONJ in early reports. The extracted teeth frequently had periodontal or periapical disease. When periodontal or apical disease is present and antiresorptive drugs are taken, a risk for ONJ exists. Hence an oral exam is recommended prior to starting the drugs and during the course of drug administration. Early resolution of oral inflammation is advised. A 2014 study identified an *Actinomyces* species in biopsied specimens of necrotic bone, an uncommon microorganism associated with oral infection. Studies have also identified fungi and viruses within the ONJ infection requiring “sophisticated therapies to combat the multiorganism ONJ-associated biofilm.”

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### Animal Model Research

The first animal studies did not consistently result in ONJ unless steroids were combined with bisphosphonates. The research included extraction of rodent teeth. Since that time studies have reported “mucosal ulceration, delayed healing, exposed bone and histologic necrosis and inflammation” in similar animal models receiving bisphosphonates and chemotherapy.

### Cancer Therapy Related ONJ

The risk for ONJ among patients with cancer who were given antiresorptive or antiangiogenic medications ranges from zero to 1.9 cases per 10,000 patients. When the bisphospho-
nate zolendronate is examined, the risk is higher (100 cases per 10,000 individuals or 1% of all cases), ranging between 50 to 100 times higher than cancer patients who took the placebo. Among cancer patients who took denosumab, the risk for ONJ ranges from 70 to 90 cases per 10,000 patients, a rate considered comparable to the risk of ONJ with zolendronate. The risk among cancer patients who took bevacizumab is 20 cases per 10,000.

The data represents a global prevalence ranging from <1 case per 100,000 exposed people in Germany to 11 cases per 90,000 people in Scotland. There is a once/year form of zolendronate for osteoporosis administered by IV. ONJ is very rare with this regimen. The subcutaneous administration of denosumab for osteoporosis, given every six months, has a very low risk for ONJ. The AAOMS paper reports “the risk for ONJ among patients (with osteoporosis) treated with either zolendronate or denosumab approximates the risk for ONJ of patients enrolled in placebo groups.”

Other Risk Factors
The length of time the medications are taken is a risk factor. The longer the drugs are taken, the greater the risk for MRONJ development. The case report of BRONJ in this course occurred prior to one year of drug usage. Surveys of health insurance records suggest the prevalence of BRONJ is 10 cases per 10,000 individuals, which increased to 21 cases/10,000 if the bisphosphonate was taken more than four years. The data represents a global prevalence ranging from <1 case per 100,000 exposed people in Germany to 11 cases per 90,000 people in Scotland. There is a once/year form of zolendronate for osteoporosis administered by IV. ONJ is very rare with this regimen. The subcutaneous administration of denosumab for osteoporosis, given every six months, has a very low risk for ONJ. The AAOMS paper reports “the risk for ONJ among patients (with osteoporosis) treated with either zolendronate or denosumab approximates the risk for ONJ of patients enrolled in placebo groups.”
Risk Associated with Dental Treatment

Tooth extraction or oral surgery are listed as the most common oral procedures preceding development of MRONJ, although the estimate is only 0.5% in patients who took bisphosphonates and had tooth extraction. The bisphosphonate alendronate (Fosamax®) has been linked to non-oral problems, such as femur fractures and esophageal ulceration. Since millions of people have taken an oral bisphosphonate, this represents several thousand individuals (based on over 4000 lawsuits filed against the drug manufacturer of Fosamax®). The risk of developing MRONJ when dental implants, endodontic or periodontal procedures are provided is unknown, however the AAOMS committee judged the risk to be comparable to the risk from tooth extraction. Denture use is associated with an increased risk for ONJ when cancer patients received zolendronate by IV administration. Among cancer patients with MRONJ who had preexisting infection or inflammation, oral disease increased the risk for MRONJ.

Demographic Risk Factors

Women are more likely to develop MRONJ than men. Children who have taken bisphosphonates do not appear to be at risk as no cases of ONJ are reported in this age group. Taking concurrent corticosteroids elevates the risk, and comorbid conditions (anemia, diabetes, cancer) increase the risk if medications that predispose to ONJ are taken. It has been suggested that tobacco may increase the risk for ONJ but studies differ on the degree of risk. Studies investigating genetic factors in the development of MRONJ are ongoing and suggest a possible relationship.

Management Strategies of AAOMS Update

Physicians expecting to prescribe any medication associated with ONJ should alert the patient’s dentist regarding oral procedures to bring the mouth to optimum health before the drug(s) are administered. This practice might reduce the risk of ONJ and several studies support this view. Dentists are advised to provide a thorough clinical exam with radiographs (as needed) and eliminate any infection or potential infection to prevent future oral problems. Preventive dental services and a regular maintenance schedule are recommended. Tables 1 and 2 provide guidance for dental management based on various patient characteristics.

Drug Holiday: Cessation of medication associated with MRONJ is suggested when procedures that involve osseous trauma are needed. This has been referred to as “taking a drug holiday”. The AAOMS position statement did not find evidence to support a drug holiday. However the AAOMS statement was published prior to a prospective cohort study in Korea that found when a drug holiday was taken during dental procedures in patients with MRONJ, the prognosis was improved. The authors recommend drug cessation for more than four months prior to oral surgical procedures.

Cancer patients: Individuals with cancer taking anticancer drugs must not cease taking medications. The oral condition should be monitored for health frequently and inflammation treated early.

For patients about to initiate IV administered antiresorptive or antiangiogenic treatment for cancer, the goal is to reduce the potential for oral surgery by eliminating oral infection early in the chemotherapy regimen. Non-restorable teeth or those with a poor prognosis should be removed. If antiresorptive/antiangiogenic therapy has already started, the crown of a non-restorable tooth can be removed and the pulp treated with a root canal. This may allow the tooth to exfoliate naturally. Any conditions needing surgery should be completed early in the treatment or before the antiresorptive/antiangiogenic drugs are administered. If possible, drug therapy should be delayed until the mucosa has an epithelial covering. Preventive procedures, caries control and conservative restorative procedures can be provided. If dentures are present they must be examined for fit and function and adjusted, as needed, to ensure tissue health and lack of irritation. Oral hygiene and regular dental examinations should be stressed. Dental implant procedures are not recommended, although there is no data regarding the risk of ONJ after implant placement. One early case report of loss of implants in a patient taking alendronate has been published.

Osteoporosis or Osteopenia: For patients about to receive medications associated with ONJ for osteoporosis, education regarding the potential risk for ONJ should be provided. Strong clinical research is still lacking regarding the actual risk, however a low prevalence of disease exists. Patients should be made aware that the risk increases the longer the drugs are taken. Bisphosphonates should not be taken for more than four years, as studies show the beneficial effects do not increase beyond this time period. There is no maximum time period for denosumab administration at this time. It is known that ONJ can develop spontaneously or after minor trauma, however these cases appear to be less severe. Elective alveolar surgery, including periodontal procedures, is not contraindicated in patients taking bisphosphonates for less than four years who have no symptoms of ONJ. If dental implants are planned, the patient should be aware of the small risk for ONJ or implant failure. Recommending a drug holiday may be considered when traumatic oral procedures are needed. In the past a recommendation was made to assess systemic markers of bone turnover. This test has not been validated to reduce the risk of ONJ and is not recommended in the 2014 AAOMS position statement. Patients must understand the importance of maintaining oral health and good oral hygiene, along with having regular oral examinations.

For individuals who have taken bisphosphonates less than four years, have taken corticosteroids or antiangiogenic medications, and who need oral surgery, the prescribing physician/provider should be consulted for consideration of a drug holi-
day (for two months prior to and three months after planned surgery). Antiresorptive therapy can be continued after surgically treated areas have healed.

When bisphosphonate therapy has been taken for more than four years, patient advice should include consideration of cessation of therapy. If oral surgery is required, the drug should be stopped and not restarted until healing has occurred.6

Established MRONJ

For patients with established MRONJ, the objective is to eliminate pain, control infection and minimize progression of the necrosis. Elective dental surgery should be avoided. Loose sequestra should be removed gently to promote tissue healing.5 Hyperbaric oxygen treatments may be successful as an adjunctive therapy. Studies are continuing to discover useful therapies for advanced ONJ. In 2013 successful restoration of bone using weekly injections of teriparatide (Forteo®) was reported in BRONJ. There was complete healing of bone in an area of the mandible previously scheduled for resection.12 This research must be verified in larger clinical studies, but is promising.

Patient Education

According to the 2014 AAOMS guidelines6, patients must understand the importance of maintaining oral health and good oral hygiene, along with having regular oral examinations, when these drugs are taken. When osteoporosis exists, patients should be informed the risk for ONJ increases the longer the drugs are taken. Educating patients to avoid taking bisphosphonates for more than four years is advised. Dental hygiene procedures and nonsurgical dental treatments are safe when these drugs are taken and no adverse effects have developed. However patients should be advised to quickly report any pain or exposed bone that develops.

Conclusions

The case report illustrates the quandary an affected individual goes through while trying to find a medical professional to diagnose the symptoms of MRONJ. The relationship between development of the condition and taking a corticosteroid, such as prednisone, with a bisphosphonate is illustrated. Although most cases involve taking anti-resorptive drugs for more than one year, the condition can develop when the drug has been taken less than a year. Features of this and other reported cases of MRONJ include infection with Actinomycetes bacteria. Bisphosphonates bind irreversibly to bone and stay within the bone for many years, leading to potential for multiple exacerbations of the condition over time.

Management includes patient education regarding the value of preventing oral disease and having frequent oral exams to identify dental disease early. Medication use and length of therapy should be evaluated and patients educated to avoid taking bisphosphonates for more than four years. The patient should understand the value of avoiding situations that promote the need for oral surgical procedures. More research is needed regarding risk factors for MRONJ and prevention strategies to reduce the risk. It is still unknown why some people develop the condition while others do not, and why some people develop ONJ although at risk medications were taken for less than a year.

References


Author profile

Frieda Atherton Pickett, RDH, MS, graduated from the Masters of Science, Dental Hygiene Education program at the University of Missouri–Kansas City in 1970 and has taught in, directed programs for and authored texts and courses for the dental hygiene profession over the past 45 years. Frieda has received many awards and lectures internationally. Ms. Pickett has served as a test constructor for the American Dental Association Dental Hygiene National Board Committee. She continues to investigate new products and methods to deliver oral services and currently serves on the Access to Care Committee for the Tennessee Dental Hygienists’ Association. Frieda can be reached at fpickett2@gmail.com.

Author Disclosure

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1. All of the following nomenclature terms have been used to describe osteonecrosis of the jaw associated with drugs except:
   a. Bisphosphonate associated radionecrosis of the jaw (RON)
   b. Antiresorptive agent–induced osteonecrosis of the jaw (ARONJ)
   c. Medication related osteonecrosis of the jaw (MIRONJ)
   d. Bisphosphonate–related osteonecrosis of the jaw (BIRONJ)

2. The first drug reported to be associated with bisphosphonate-related osteonecrosis of the jaw was:
   a. Alendronate (Fosamax®)
   b. Bevacizumab (Avastin®)
   c. Denosumab (Prolia®)
   d. Raloxifene (Evista®)

3. Development of osteonecrosis of the jaw is related to all of the following factors except:
   a. Female gender
   b. Taking antiresorptive medications
   c. Taking antiangiogenic agents
   d. Taking single therapy corticosteroid drugs

4. The initial description of BRONJ, used for workers in a matchstick factory, was called:
   a. Focal abscess
   b. Fasculi
   c. Phossy jaw
   d. Radionecrosis

5. In the condition identified in question #4, what was the proposed etiology of the condition?
   a. Iodine
   b. Phosphorus
   c. Sulphur
   d. Zinc

6. Which of the following drugs has been implicated in osteonecrosis of the jaw?
   a. Alendronate (Fosamax®)
   b. Denosumab (Prolia®)
   c. Bevacizumab (Avastin®)
   d. All of the above

7. Which of the following bisphosphonate drugs is administered once yearly for osteoporosis?
   a. Alendronate (Fosamax®)
   b. Zolendronate (IV administration)
   c. Denosumab (Prolia®)
   d. Raloxifene (Evista®)

8. Which of the following factors increases the risk for ONJ?
   a. Receiving antiresorptive medications plus corticosteroids
   b. Receiving antiresorptive medications and having tooth extraction
   c. Receiving cancer chemotherapy
   d. Both a and b

9. The American Dental Association, Council on Scientific Affairs, Expert Committee on Antiresorptive Agents called for a name change from BRONJ to:
   a. Antiresorptive agent induced osteonecrosis of the jaw (ARONJ)
   b. Antigangliogenic related osteonecrosis of the jaw (ARONJ)
   c. Chemotherapy related osteonecrosis of the jaw (CRONJ)
   d. None of the above

10. In the case report cited, which of the following factors does not correspond with general factors associated with BRONJ?
    a. Patient took alendronate
    b. Alendronate was taken less than a year before BRONJ developed
    c. Corticosteroid therapy was taken concurrently with alendronate
    d. Osteonecrosis of the jaw recur ed a few years following the initial exacerbation

11. Antibiotic therapy in MIRONJ is directed to eliminate which one of the following microorganisms?
    a. Actinomyces Streptococci
    b. Bacillus Streptococci
    c. Spironucleus
    d. Myotic organisms

12. Avascular necrosis is a condition associated with:
    a. Numbness of the tongue
    b. Osteonecrosis of the jaw
    c. Taste disturbances
    d. Clotting irregularities

13. Management strategies to reduce the risk for developing ONJ include all of the following except:
    a. Education to avoid need for surgical procedures
    b. Education to take antiresorptive drugs for no more than ten years
    c. Scheduling regular oral examinations
    d. Recommendation to have dental procedures that promote oral health

14. Bisphosphonates are potent inhibitors of:
    a. Menopause
    b. Metastatic disease
    c. Osteoclastic bone resorption
    d. Calcium deposition

15. The prevalence of ONJ in cancer patients using intravenous bisphosphonates is:
    a. 1% (100 in 10,000)
    b. 15% (1500 in 10,000)
    c. 25% (2500 in 10,000)
    d. 50% (5000 in 10,000)

16. Recent cases of ONJ have been reported in cancer patients being treated with which of the follow products?
    a. Antiprostaglandins
    b. Antihistamines
    c. Antiangiogenics
    d. Corticosteroids

17. Angiogenesis is the:
    a. Formation of new blood vessels
    b. Destruction of blood vessels
    c. Development of angina
    d. Formation of blood vessels

18. What is the mechanism of action of bevacizumab (Avastin®)?
    a. Blocks endorphins
    b. Encourages formation of blood vessels
    c. Discourages formation of blood vessels
    d. Increases bone formation to block metastasis of cancer

19. Which of the following drugs has been reported to increase bone formation in ONJ?
    a. Alendronate (Fosamax®)
    b. Bevacizumab (Avastin®)
    c. Denosumab (Prolia®)
    d. Teriparatide injection (Forteo®)

20. Denosumab is described as:
    a. The drug with the highest percentage of ONJ
    b. The first drug to be developed for osteoporosis
    c. A fully human monoclonal antibody
    d. The drug of choice to treat ONJ

21. The management strategy for the patient who plans to start bisphosphonate therapy includes all of the following except:
    a. Communicate with physician to encourage referral of patients for dental exam
    b. Educate about the low risk for ONJ
    c. Encourage dental treatment to eliminate inflammation and infection
    d. Avoiding use of surgical procedures

22. The management strategy for the patient who has taken bisphosphonate therapy for more than four years includes all of the following except:
    a. Educate to take a drug holiday before oral surgery
    b. Consult with physician about patient stopping the drug
    c. Advise keeping regular periodontal maintenance care
    d. Recommend dental implants after tooth extraction

23. All of the following bacteria are common causes of oral infection except:
    a. Treponema denticola
    b. Actinomycetes israelii
    c. Aggregatibacter actinomycetemcomitans
    d. Porphyromonas gingivalis

24. Sequestrum is a term used to describe:
    a. Fused ulceration
    b. Multiple mucosal pepticulie
    c. Sclerses of unattached bone
    d. None of these

25. All of the following are part of the defined diagnosis of MIRONJ except:
    a. Current or previous treatment with antiresorptive or antiangiogenic agents
    b. Exposure bone or bone that can be probed through
    c. Itraoral or extroral sinus tract in the maxillofacial region that has persisted for more than six weeks
    d. No history of treatment with radiation of the jaws
    e. History of metastatic lesions to the jaws

26. ONJ can develop in patients who have not taken antiresorptive or antiangiogenic agents if which of the following is present?
    a. Poor plaque control
    b. History of trauma to jaw
    c. Undiagnosed cysts in tooth root area
    d. None of the above

27. Proposed hypotheses for ONJ include all of the following except:
    a. Altered bone remodeling or oversuppression of bone resorption
    b. Angiogenesis inhibition
    c. Mutation of osteoblasts
    d. Vitamin D deficiency

28. When periodontal or apical disease is present and antiresorptive drugs are taken, the patient is at risk for which of the following conditions?
    a. Chronic xerostomia
    b. Dental decay
    c. Mucostral ulceration
    d. Necrotic exposed bone

29. Research suggests a potential additive toxic effect when antiangiogenic drugs are taken and when which of the following were taken in the past?
    a. Antiviral agents
    b. Bisphosphonates
    c. Corticosteroids
    d. Immune enhancing agents

30. Which one of the following outcomes occurred in cancer patients who developed osteonecrosis of the jaw?
    a. Decreased pain associated with ONJ
    b. Increased mortality from the malignancy
    c. Increased survival rate from malignancy
    d. Increased vascular infection
# Update on Medication Related Osteonecrosis of the Jaw

## Educational Objectives

1. Define the terms used to describe osteonecrosis of the jaw (ONJ) associated with various drugs.
2. Explain the factors that can lead to development of medication related ONJ (MARNJ).
3. List the various medications implicated in ONJ and mechanisms of action of these drugs.
4. Describe prevention measures and management strategies when drugs associated with ONJ are reported on the health history.

## Course Evaluation

1. Were the individual course objectives met?
   - Objective #1: Yes  No
   - Objective #2: Yes  No
   - Objective #3: Yes  No
   - Objective #4: Yes  No

2. To what extent were the course objectives accomplished overall?
   - 5 4 3 2 1 0

3. Please rate your personal mastery of the course objectives.
   - 5 4 3 2 1 0

4. How would you rate the objectives and educational methods?
   - 5 4 3 2 1 0

5. How do you rate the author's grasp of the topic?
   - 5 4 3 2 1 0

6. Please rate the instructor's effectiveness.
   - 5 4 3 2 1 0

7. Was the overall administration of the course effective?
   - 5 4 3 2 1 0

8. Please rate the usefulness and clinical applicability of this course.
   - 5 4 3 2 1 0

9. Please rate the usefulness of the supplemental weblogography.
   - 5 4 3 2 1 0

10. Do you feel that the references were adequate?
    - Yes  No

11. Would you participate in a similar program on a different topic?
    - Yes  No

12. If any of the continuing education questions were unclear or ambiguous, please list them.

13. Was there any subject matter you found confusing? Please describe.

14. How long did it take you to complete this course?

15. What additional continuing dental education topics would you like to see?

# Academy of Dental Therapeutics and Stomatology

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**COURSE OBJECTIVES**

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