Compiled by R.L.Wynn (October 2013)

Updated summary of drugs and other risk factors associated with osteonecrosis of the jaw.

The bisphosphonate group of drugs has been associated with a risk of osteonecrosis of the jawbone (ONJ) for the past 10 years. The definition of bisphosphonate associated ONJ is the following. Defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider, in a patient who is receiving or been exposed to a bisphosphonate and not had radiation therapy. Now we can add more drugs to this definition and a recent review out of Roswell Park Cancer Institute and the State University of New York School of Dental Medicine, Buffalo published in the journal Oral Oncology has described those drugs which pose a risk. The list of drugs and other risk factors as presented in this report are described below.

The review can be found at Hinchy NV et al. Osteonecrosis of the jaw – Prevention and treatment strategies for oral health professionals. Oral Oncology 2013; 49: 878-886.

The following table compiles the latest list of drugs, according to the published review, associated with a risk for ONJ. The FDA approved medical use is listed with each drug.

Antiangiogenic Drugs

Bevacizumab (Avastin)

Metastatic carcinoma of colon or rectum; metastatic nonsquamous, non-small cell lung cancer; breast cancer; kidney cancer.

Sunitinib (Sutent)

Advanced renal cell carcinoma; gastrointestinal stromal tumors; advanced pancreatic neuroendocrine tumors.

Non-bisphosphonate antiresorptive drug (Anti-RANKL drug)

Denosumab (Prolia)

Osteoporosis

To increase bone mass during nonmetastatic prostate cancer androgen deprivation therapy and breast cancer adjuvant aromatase inhibitor therapy.

Denosumab (Xegeva)

Prevention of skeletal metastases from solid tumors (breast, prostate, or lung)

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Bisphosphonates - Intravenous

Zoledronic acid (Zometa)

used for prevention of bone metastases from breast, prostate and multiple myeloma management; prevention of hypercalcemia of malignancy

Palmidronate (Aredia)

used for prevention of bone metastases from breast, prostate and multiple myeloma management; prevention of hypercalcemia of malignancy

Zolendronic acid (Reclast)

Management of osteoporosis

Bisphosphonate – Intravenous and Oral

Ibandronate (Boniva)

Management of osteoporosis

Bisphosphonates – Oral

Alendronate (Fosamax)

Osteoporosis; Paget's disease of the bone

Risedronate (Actonel)

Osteoporosis; Paget's disease of the bone

Etidronate (Didronel)

Paget's disease of the bone

Tiludronate (Skelid)

Paget's disease of the bone

Clodronate (Bonefas) –Canada

Hypercalcemia of malignancy

Patients at risk for ONJ

The mechanism of drug related ONJ and reason for localization to the jaws has not been established. Hypotheses include altered bone remodeling, inhibition of angiogenesis, constant microtrauma, soft tissue bisphosphonate toxicity, bacterial infection and local inflammation. Risk factors include not only

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the drugs shown in the table, but also systemic co-morbidities as well as localized oral health conditions and dental hygiene habits. The etiology seems to be multifactorial.

Drug related risk factors

Anti-angiogenic agents

Sunitinib (Sutent) exhibits antitumor and antiangiogenic properties by inhibiting multiple receptor tyrosine kinase pathways. According to the Hincy et al review, recent studies have attributed some cases of ONJ to sunitib use.

Bevacizumab (Avastatin) is a recombinant, humanized monoclonal antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).Three case reports describe the development of ONJ in association with bevacizumab therapy. All three cases were cancer patients treated with bevacizumab 10 mg/kg every 2 weeks and 15 mg/kg every 3 weeks (Estilo, 2009; Greuter, 2008). Another report showed that a combination of bisphosphonates and antiangiogenic factors (primarily bevacizumab) induces ONJ more frequently than bisphosphonates alone. Of the 25 patients receiving concurrent treatment with bisphosphonates and the antiangiogenic drug bevacizumab, four developed ONJ (16%). Of the 91 patients receiving bisphosphonates without antiangiogenic factors, one developed ONJ (1.1%), a significant statistical difference (Christodoulou, 2009).

Christodoulou C, Pervena A, Klouvas G, et al, "Combination of Bisphosphonates and Antiangiogenic Factors Induces Osteonecrosis of the Jaw More Frequently Than Bisphosphonates Alone," *Oncology*, 2009, 76(3):209-11.[PubMed 19212145]

Estilo CL, Fornier M, Farooki A, et al, "Osteonecrosis of the Jaw Related to Bevacizumab," *J Clin Oncol*, 2008, 26(24):4037-8.[PubMed 18711196]

Greuter S, Schmid F, Ruhstaller T, et al, "Bevacizumab-Associated Osteonecrosis of the Jaw," *Ann Oncol*, 2008, 19(12):2091-2.[PubMed 18977851]

Non-bisphosphonate antiresorptive drug (Anti-RANKL drug)

Denosumab (Prolia; Xgeva) is a monoclonal antibody with affinity for nuclear factor-kappa ligand (RANKL). Osteoblasts secrete RANKL; RANKL activates osteoclast precursors and subsequent osteolysis which promotes release of bone-derived growth factors, such as insulin-like growth factor-1 (IGF1) and transforming growth factor-beta (TGF-beta), and increases serum calcium levels. Denosumab binds to RANKL, blocks the interaction between RANKL and RANK (a receptor located on osteoclast surfaces), and prevents osteoclast formation, leading to decreased bone resorption and increased bone mass in osteoporosis. In solid tumors with bony metastases, RANKL inhibition decreases osteoclastic activity leading to decreased skeletal related events and tumor-induced bone destruction. In giant cell tumors of the bone (which express RANK and RANKL), denosumab inhibits tumor growth by preventing RANKL

from activating its receptor (RANK) on the osteoclast surface, osteoclast precursors, and osteoclast-like giant cells.

In head-to-head comparison trials of denosumab and zoledronate (a bisphosphonate) for the treatment of bone metastasis in patients with cancer, 20 cases of ONJ were detected out of a total of 1026 subjects (2.0%) exposed to denosumab. There were 14 cases of ONJ observed out of a total of 1020 subjects (1.4%) exposed to zoledronate (Kyrgidis, 2010). The case of a 60-year old male cancer patient who developed ONJ after treatment with denosumab has been published (Taylor, 2010). In that report, the patient participated in a trial for a phase 3 study of denosumab. The patient had never been prescribed a bisphosphonate medication before treatment with denosumab. Clinical and radiological features of the lesion were diagnostic of probable ONJ. After discontinuation of the denosumab, the patient was treated with antibiotics and chlorhexidine rinses for a week. The necrotic bone sequestered 12 months later, and 15 months after initial presentation, the mucosa had healed with no further symptoms. Another case reported the development of ONJ in a 65-year old women being treated for giant cell tumor with denosumab. Although the patient was medically compromised and on multiple medications, the authors proposed that a common thread in ONJ development is inhibition of osteoclastic activity, mediated in this case by denosumab.

Kyrgidis A and Toulis KA, "Denosumab-Related Osteonecrosis of the Jaws," *Osteoporos Int*, 2010, [epub ahead of print].[PubMed 20306021]

Taylor KH, Middlefell LS, and Mizen KD, "Osteonecrosis of the Jaws Induced by Anti-RANK Ligand Therapy," *Br J Oral Maxillofac Surg*, 2010, 48(3):221-3.[PubMed 19836866]

Bisphosphonates – Intravenous

The American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws, 2009 update, stated that I.V. bisphosphonate exposure in the setting of managing malignancy remains the major risk factor for the development of ONJ. After reviewing case series, case-controlled studies, and cohort studies, the estimates of the cumulative incidence of I.V. bisphosphonate-associated ONJ ranges from 0.8% to 12%.

Ruggiero SL, Dodson TB, Assael LA, et al, "American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws-2009 Update," *J Oral Maxillofac Surg*, 2009, 67(5 Suppl):2-12.[PubMed 19371809]

Zoledronic acid (Reclast) is administered once annually for the treatment of osteoporosis. A single, large prospective, placebo-controlled study established its efficacy for this indication through 3 years of treatment (Black, 2007). Two cases of ONJ were reported, one each in the treatment and control groups, suggesting a low risk of ONJ with this treatment protocol through 3 years.

Black DM, Delmas PD, Eastell R, et al, "Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis," *New Engl J Med*, 2007, 356(18):1809-22.[PubMed 17476007]

Bisphosphonates – Oral

According to the 2011 report by the American Dental Association (ADA), the incidence of bisphosphonate-associated ONJ remains low and the benefits of using oral bisphosphonates significantly outweighs the risk of developing bisphosphonate-associated ONJ for treatment and prevention of osteoporosis and cancer treatment (Hellstein, 2011). The full 47 page report can be accessed at http://www.ada.org/sections/professionalResources/pdfs/topics_ARONJ_report.pdf.

The ADA review of 2011 stated the incidence of oral bisphosphonate-associated ONJ was one case for every 1000 individuals exposed to oral bisphosphonates (0.1%) (Hellstein, 2011).

Hellstein JW, Adler RA, Edwards B, et al, "Managing the Care of Patients Receiving Antiresorptive Therapy for Prevention and Treatment of Osteoporosis: Executive Summary of Recommendations From the American Dental Association Council on Scientific Affairs," *J Am Dent Assoc*, 2011, 142(11):1243-51.[PubMed 22041409]

Dental risk factors

According to the review, patients exposed to oral bisphosphonates for many years are considered at high risk of ONJ in the advent of oral trauma and/or oral surgery. In approximately 60% of ONJ cases reported, dental extraction was identified as a causative factor. In addition to tooth extraction, risk factors may include other invasive dental procedures such as dental implants and boney surgery. Other dental factors may include poor oral hygiene and ill-fitting dentures.

Low risk dental interventions include adult prophylaxis, routine restorative dentistry and endodontics without aggressive instrumentation.

Systemic risk factors

The review described a number of systemic risk factors. They include underlying oncologic disease such as breast cancer, prostate cancer, or multiple myeloma. Other comorbidities are diabetes and osteoporosis. Other factors include alcohol and tobacco useage and advanced age. It was suggested that there may be a possible association of hypothyroidism and ONJ. Many of the medications implicated in ONJ are often prescribed in combination with each other or with other chemotherapy drugs and/or radiation therapy. The review cited several studies showing that the risk of ONJ is higher when drugs like bevacizumab, sunitinib, thalidomide and corticosteroids are used in conjunction with bisphosphonates.

Corticosteroid therapy: The review states that corticosteroids increase the risk of ONJ. Patients with malignant disease and current steroid exposure are classified as high risk of ONJ, irrespective of intravenous bisphosphonate use. Corticosteroids such as prednisone and prednisolone are used routinely in cancer treatment. The mechanism of steroid-related osteonecrosis has not been established. However, the review states that bone destruction is the result of compromised blood flow leading to the death of osteocytes and preventing normal repair of bone.

Abstract

Full text links

QUINTESSENCE

Quintessence Int. 2016;47(5):433-40. doi: 10.3290/j.qi.a35263.

Medication-related osteonecrosis of the jaw after once-a-year intravenous zoledronic acid infusion for osteoporosis: Report of eight cases.

Favia G, Tempesta A, Limongelli L, Crincoli V, Maiorano E.

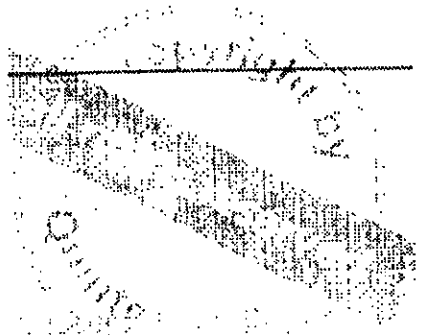

Table 1 Patients' data

Case	Age/ gender	Medication/time	Trigger event	Location	Systemic factors	MRONJ stage (AAOMS)	Treatment
	53/F	2 zoledronic acid infusions	Spontaneous	Mandibular retromolar trigone	Gastric cancer, polychemotherapy	2	Antibiotics, surgery
	62/F	1 zoledronic acid infusion; previous oral BPs for 7 years	Tooth extraction	Maxillary alveolar ridge	None	2	Antibiotics, surgery
Case 1 (Fig 1)	63/F	2 zoledronic acid infusions	Tooth extraction	Mandibular alveolar ridge	None	1	Antibiotics, surgery
Case 2 (Fig 2)	60/F	2 zoledronic acid infusions	Tooth extraction	Mandibular alveolar ridge	None	1	Antibiotics, surgery
Case 3 (Fig 3)	57/F	2 zoledronic acid infusions; previous oral BPs for 3 years	Spontaneous	Mandibular retromolar trigone	None	1	Antibiotics, surgery
Case 4 (Figs 4a and 4b)	54/F	1 zoledronic acid infusion; previous oral BPs for 4 years	Spontaneous	Mandibular retromolar trigone	Rheumatoid arthritis, corticosteroid use	1	Antibiotics, surgery
Case 5 (Figs 5a and 5c)	50/F	1 zoledronic acid infusion; previous oral BPs for 3 years	Spontaneous	Mandibular alveolar ridge	Rheumatoid arthritis, corticosteroid use	1	Antibiotics, surgery
Case 6 (Figs 6a and 6b)	58/F	1 zoledronic acid infusion; previous oral BPs for 3 years	Traumatic fixed prosthesis	Mandibular alveolar ridge	None	1	Antibiotics, surgery

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Osteonecrosis of the Jaw in the United States Food and Drug Administration's Adverse Event Reporting System (FAERS)

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Table 1. Demographics of the Osteonecrosis of the Jaw Cases Reported in FAERS Between the First Quarter of 2010 and the First Quarter of 2014

	All ONJ cases (n = 17,119)	SRE (n = 6930)	Osteoporosis (n = 4760)
Age (years) (mean ± SD)	62.2 ± 12.1	66.5 ± 15.4	63.0 ± 11.8
Male (%)	30.3%	41.2%	10.0%
Country reported			
United States	69.7%	55.7%	84.2%
Japan	6.8%	13.0%	1.6%
Germany	5.6%	6.5%	3.0%
Italy	3.6%	7.1%	0.5%
France	1.5%	2.3%	0.9%
United Kingdom	1.5%	1.7%	0.6%
Medications			
Bisphosphonates			
Zoledronate	11490 (67.1%)	6200 (89.5%)	809 (17.0%)
Alendronate	7307 (42.7%)	350 (5.1%)	4020 (84.5%)
Pamidronate	5251 (30.7%)	2485 (35.9%)	330 (6.9%)
Risedronate	827 (4.8%)	93 (1.3%)	566 (11.9%)
Ibandronate	786 (4.6%)	60 (0.9%)	600 (12.6%)
Clodronate	33 (0.2%)	19 (0.3%)	9 (0.2%)
Etidronate	28 (0.2%)	1 (0.01%)	23 (0.5%)
RANKL inhibitor			
Denosumab	1184 (6.9%)	441 (6.4%)	376 (7.9%)
Antiangiogenic agents			
Bevacizumab	703 (4.1%)	395 (5.7%)	22 (0.5%)
Sunitinib	418 (2.4%)	292 (4.2%)	na
Sorafenib	90 (0.5%)	41 (0.6%)	na
Pazopanib	10 (0.1%)	9 (0.1%)	na
Axitinib	9 (0.1%)	8 (0.1%)	na
m-TOR inhibitor			
Everolimus	84 (0.5%)	71 (1%)	3 (0.1%)
Temsirolimus	28 (0.2%)	18 (0.3%)	1 (0.02%)

ONJ = osteonecrosis of the jaw; SRE = skeletal related events.
Values presented are n (%) unless stated otherwise.
Note that not all ONJ cases had clear indications for use of medications.

Table 2. Drugs Associated With ONJ and the Reporting Odds Ratios in FAERS

Drug	Drug class	OR	95% Confidence interval	p Value
Pamidronate	BP	498.9	(475.2–523.8)	< 0.0001
Zoledronate	BP	171.7	(166.1–177.6)	< 0.0001
Alendronate	BP	63.6	(61.6–65.7)	< 0.0001
Clodronate	BP	33.0	(22.8–47.7)	< 0.0001
Risedronate	BP	16.6	(15.4–17.8)	< 0.0001
Ibandronate	BP	16.3	(15.1–17.6)	< 0.0001
Denosumab	RANKL inhibitor	13.8	(13.0–14.7)	< 0.0001
Etidronate	BP	12.3	(8.4–18.0)	< 0.0001
Sunitinib	Antiangiogenic	4.6	(4.2–5.1)	< 0.0001
Bevacizumab	Antiangiogenic	4.5	(4.2–4.9)	< 0.0001
Temsirolimus	m-TOR inhibitor	3.1	(2.2–4.6)	< 0.0001
Sorafenib	Antiangiogenic	1.5	(1.2–1.9)	< 0.0001
Everolimus	m-TOR inhibitor	1.4	(1.2–1.8)	0.0008
Pazopanib	Antiangiogenic	1.3	(0.7–2.5)	0.38
Axitinib	Antiangiogenic	0.8	(0.4–1.5)	0.49

OR = reporting odds ratio; BP = bisphosphonates; RANKL = human monoclonal antibody to the receptor activator of nuclear factor-κB ligand; m-TOR inhibitor = mammalian target of rapamycin inhibitor.

Table 7. Clinical staging for osteonecrosis of the jaw.

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Stage	Clinical description
1	• Asymptomatic • Exposed bone on mandible or maxilla • No evidence of significant adjacent or regional soft tissue inflammation or secondary infection
2	• Painful • Exposed bone on mandible or maxilla • Adjacent or regional soft tissue inflammation or secondary infection
3	• Painful • Exposed bone on mandible or maxilla • Adjacent or regional soft tissue inflammation or secondary infection • extra-oral fistula or oral antral fistula or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus

8. How should ONJ be managed?

Stage 1:

Treatment consists primarily of conservative therapy focusing on improving oral hygiene, treating active dental and periodontal disease, topical antibiotic mouth rinses.

Stage 2:

Treatment as in Stage 1, with addition of symptom management, systemic antibiotic therapy if infection is suspected and consideration of surgical debridement.

Stage 3:

Treatment as in Stage 2, with addition of surgical debridement/resection which may involve jaw reconstruction. Management is governed by multiple factors including severity of symptoms, functional impairment, and overall patient prognosis.

Type: evidence-based. Grade of recommendation: D.

6. Can ONJ be prevented and what is the role of drug interruption?

Identification and treatment of dental disease prior to initiation of anti-resorptive therapy if possible is recommended. Evolving data suggest optimizing oral hygiene prior to initiating anti-resorptive therapy may reduce the incidence of ONJ.

Type: evidence-based. Grade of recommendation: C.

There is insufficient evidence to suggest that interrupting anti-resorptive therapy before a minor oral surgical procedure will alter the risk of developing ONJ.

In those at high risk for the development of ONJ including cancer patients receiving high-dose BP or Dmab therapy consideration should be given to withholding anti-resorptive therapy following extensive oral surgery until the surgical site heals with mature mucosal coverage.

Type: consensus-based. Grade of recommendation: D.

Therapy can be resumed following clinical evidence of mature soft tissue closure.

Type: consensus-based. Grade of recommendation: D.

Where we are today with oral BPs

1. Incidence 0.1% ONJ in Fosamax users
- 2. Probably be the same in Boniva and Actonel users
- 3. Inc risk with 3 years or more exposure, over 60 years of age, taking prednisone, and undergoing extractions
- 4, palmidronate (Aredia) in CA = 4% ; zoledronic (Zometa) in CA = 10 %

Where we are today

5. CTX test not universally accepted
6. Drug Holiday may be beneficial in select pts prior to dental surgery to reduce risk of ONJ
7. ONJ can occur spontaneously
8. New drug class (Prolia) may be associated with ONJ – Anti-RANKL agents 1-2%
9. Antiangiogenic drugs associated with ONJ

Where we are today

- 10. More reports of once-a-year infusion with zoledronic acid (Reclast) and ONJ
- 11. Another new class of drugs associated with ONJ – called m-TOR inhibitors
  - Everolimus, Temsirolimus – used in treating various cancers including breast cancer

Antibiotic Stewardship

Valley Study Club, Winchester VA, R.L.Wynn, Professor, U Maryland Dec 14, 2017

Considerations for responsible antibiotic use in dentistry

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Alexander Fleming's discovery of penicillin in 1928 is one of the greatest medical advancements in history.[1] The introduction of antibiotics meant that infectious diseases that were once deadly could now be cured. Since 1928, countless lives have been saved, and antibiotics have been recognized as miracle drugs. However, as antibiotic use has become more prevalent, so have antibiotic-resistant bacteria and adverse events associated with their use.[2,3] In his 1945 Nobel Lecture, Fleming warned of the danger of overreliance on antibiotics and the threat of bacteria developing resistance.[3]

Misuse and overuse of antibiotics have contributed to selective pressure on bacteria to adapt to the antibiotics intended to kill them; antibiotic resistance is now one of our most serious global health threats.[2] Every year in the United States, at least 2 million people become infected with antibiotic-resistant bacteria, and approximately 23,000 people die as a direct result of these infections.[2] Concurrently, there has been a decrease in research and development of new antibiotics, which has compounded the antibiotic resistance crisis, making treatment of infections in some patients challenging.[4-6]

UNINTENDED CONSEQUENCES OF ANTIBIOTIC USE

Antibiotics should be treated as a resource that is naturally limited in supply. Clinicians must consider the potential effect of their antibiotic prescribing choices on the larger community, as well as on individual patients, because there are risks to both. Each time an antibiotic is used, there is an increased risk of developing a subsequent antibiotic-resistant infection in both the patient taking the antibiotic and those in the community who come into contact with the patient. There are several deadly bacteria for which few antibiotics are effective, making treatment of infections associated with these pathogens more costly and less successful.[2] We have begun to enter a postantibiotic era in which certain infectious diseases are no longer treatable and the risk from resistant organisms precludes chemotherapeutic treatment, bone marrow and organ transplant, and many elective surgeries.

Furthermore, antibiotics are not the innocuous drugs that some clinicians and many patients perceive them to be. An estimated 1 in every 5 emergency department visits for adverse drug events in the United States is for antibiotic-related adverse events (approximately 142,000 adult visits each year).[7] Antibiotics are also the main cause of health care– and community-associated *Clostridium difficile* infections, a potentially deadly form of diarrheal disease associated with considerable costs to patients and the health care system.[7,8] Antibiotic use also disrupts the microbiome, potentially leading to other long-term consequences, such as asthma and obesity.[9]

ANTIBIOTIC PRESCRIPTIONS

Antibiotics are among the most commonly prescribed medications. However, study results indicate that 30% to 50% of prescribed antibiotics are either not necessary or not optimally prescribed.[10] Dentists write approximately 10% of all outpatient antibiotic prescriptions (approximately 25.6 million) filled in the United States each year.[11] Although there are few studies in which the investigators evaluate the appropriateness of antibiotic prescribing in dentistry, it is likely that there are opportunities to improve prescribing practices.

Results from studies in which the investigators assess physicians' knowledge, attitudes, and behaviors regarding antibiotic use indicate that patient demands and expectations, providers' perceptions related to patient expectations, fear of litigation, and diagnostic uncertainty are important factors that lead to overprescribing.[12] We can assume that similar pressures affect prescribing in dentistry. The authors of a 2000 article published in The Journal of the American Dental Association surveyed all licensed dentists practicing in Canada and found that there was confusion about antibiotic prescribing recommendations and that inappropriate prescribing practices were evident, such as improper dose and duration of therapy.[13]

BOX 1

Clinical tips for antibiotic prescribing by dentists.

PRETREATMENT CONSIDERATIONS

- Make the correct diagnosis of an oral bacterial infection.
- Recognize that antibiotics are rarely helpful for effective control of a localized oral infection.
- Therapeutic management interventions, such as incision and drainage, extraction, or endodontic therapy, are appropriate first steps in treating most oral bacterial infections. Weigh the potential benefits and risks of antibiotics before prescribing. Toxicity, allergy, adverse effects, and *Clostridium difficile* infection can occur even with a single dose.[21]
- Prescribe antibiotics (and all other prescriptions) only for patients of record.
- Prescribe antibiotics only for bacterial infections you have been trained to treat.
- Do not prescribe antibiotics for oral viral infections, fungal infections, or oral ulcerations related to trauma or aphthae.
- Understand and implement national recommendations for antibiotic prophylaxis for the medical concerns for which guidelines exist (for example, cardiac defects).
- Review the patient's medical history to
  - assess medication allergies, drug-drug interactions, and the potential for other adverse drug events;
  - review pregnancy status and medical conditions that would affect antibiotic selection.

CHAIRSIDE PRESCRIBING

- Ensure that antibiotic expertise or references are available and can be accessed during patient visits.
- Avoid prescribing based on
  - nonevidence-based historical practices;
  - patient demand or expectations;
  - convenience of clinician or patient;
  - pressure from other health care professionals.
- Make and document the diagnosis, treatment steps, and, if prescribed, the rationale for antibiotic use in the patient chart.
- Prescribe only when clinical signs and symptoms of a bacterial infection suggest systemic spread, such as fever or malaise along with localized oral swelling.
- Use the most targeted (narrow-spectrum) antibiotic for the shortest duration possible (2-3 days after the clinical signs and symptoms subside) for otherwise healthy patients.
- For empirical treatment, revise antibiotic regimens on the basis of patient progress and, if needed, culture results.
- Consider a conversation about antibiotic use with referring specialists about their own antibiotic prescribing protocols.

ENGAGING THE PATIENT

- Educate your patients about
  - taking the antibiotic exactly as prescribed;
  - taking only antibiotics prescribed for themselves;
  - not saving antibiotics for future illness.

MAINTAINING OPTIMAL PRESCRIBING PRACTICES

- Provide training to staff members to improve the probability of patient adherence to the antibiotic prescription.
- Ensure you are up to date on appropriate management of oral bacterial infections by attending continuing education courses or conferences on the topic or accessing dental journals or pharmacology texts on the topic.

SURVEILLANCE EFFORTS AND NATIONAL PRESCRIBING GUIDELINES

Because most oral conditions are managed best with operative interventions and oral hygiene procedures, there are relatively few indications for the use of systemic antibiotics in dentistry.[14] Unlike medical claims in the United States, private dental claims do not capture diagnostic codes accompanying procedures performed or prescriptions written; without the ability to connect the diagnosis of an oral infection to a prescription for antibiotics, it is difficult to assess appropriateness.

Guidelines have been published for antibiotic prophylaxis for prevention of infective endocarditis[15] and prosthetic joint infections,[16] as well as general guidance regarding the use of antibiotic therapy for dental patients.[17,18] However, there are no national guidelines for treatment of specific dental infections, so dental care providers have to decide independently when an antibiotic is indicated, which antibiotic to use, and what dose and duration to prescribe.

ANTIBIOTIC STEWARDSHIP

Antibiotic stewardship refers to activities that aim to promote the appropriate use of antibiotics, improve patient outcomes, lower costs, reduce antibiotic resistance, and decrease the spread of infections caused by multidrug-resistant organisms. An antibiotic stewardship program works to ensure that patients receive antibiotic therapy only when it is indicated and that the right drug is prescribed at the right dose for the right duration.

During a White House Forum on Antibiotic Stewardship in June 2015, more than 100 organizations made commitments to improve antibiotic prescribing over the next 5 years.[19] These planned activities were submitted to the Centers for Disease Control and Prevention.[20] The American Dental Association (ADA) pledged to provide appropriate scientific and clinical expertise to assess fully and respond to antibiotic health care issues, offer continuing education courses at professional meetings, and provide systematic reviews and up-to-date scientific information on the proper use of antibiotics in online resources.

The following are suggested initial steps to take to understand, develop, and support antibiotic stewardship better in dentistry:

- identify data sources that can be used to understand better and characterize antibiotic prescribing by dentists;

CAUSES OF ODONTOGENIC INFECTIONS

Most acute orofacial infections are of odontogenic origin. Dental caries, resulting in infection of dental pulp, is the leading cause of odontogenic infection.

The major causative organisms involved in dental caries have been identified as members of the viridans (alpha-hemolytic) streptococci and include *Streptococcus mutans*, *Streptococcus sobrinus*, and *Streptococcus milleri*. Once the bacteria have breached the enamel they invade the dentin and eventually the dental pulp. An inflammatory reaction occurs in the pulp tissue resulting in necrosis and a lower tissue oxidation-reduction potential. At this point, the bacterial flora changes from predominantly aerobic to a more obligate anaerobic flora. The anaerobic gram-positive cocci (*Peptostreptococcus* species), and the anaerobic gram-negative rods, including *Bacteroides*, *Prevotella*, *Porphyromonas*, and *Fusobacterium* are most frequently present. An abscess usually forms at the apex of the involved tooth resulting in destruction of bone. Depending on the effectiveness of the host resistance and the virulence of the bacteria, the infection may spread through the marrow spaces, perforate the cortical plate, and enter the surrounding soft tissues.

Table 2. Penicillin VK: Antibacterial Spectrum

[1]Nonresistant staphylococcus represents a small portion of community-acquired strains of *S. aureus* (5% to 15%). Most strains of *S. aureus* and *S. epidermitis* produce beta-lactamases. which destroy penicillins.

Gram-Positive Cocci

Streptococci

Nonresistant staphylococci[1]

Pneumococci

Gram-Negative Cocci

Neisseria meningitides

Neisseria gonorrhoeae

Gram-Positive Rods

Bacillus

Corynebacterium

Clostridium

Oral Anaerobes

Bacteroides

Porphyromonas

Prevotella

Peptococci

Peptostreptococci

Actinomyces

Veillonella

Eubacterium

Eikenella

Capnocytophaga

Campylobacter

Fusobacterium

Others

Table 3. Clindamycin: Antibacterial Spectrum[1]

Gram-Positive Cocci

[3]Except *S. faecalis*

[4]Some staph strains originally resistant to erythromycin rapidly develop resistance to clindamycin.

Streptococci[3]

S. aureus[4]

Penicillinase and nonpenicillinase-producing staphylococcus

S. epidermitis

Pneumococci

Anaerobes[2]

Gram-Negative Bacilli

Bacteroides species including *B. fragilis*

B. melaninogenicus

Fusobacterium species

Gram-Positive Nonspore-Forming Bacilli

Propionibacterium

Eubacterium

Actinomyces species

Gram-Positive Cocci

Peptococcus

Peptostreptococcus

Microaerophilic streptococci

Table 1. Empiric Antibiotics of Choice for Odontogenic Infections

Type of Infection	Antibiotic of Choice
3 days or less of symptoms (early)	Penicillin VK; Amoxicillin
	Clindamycin
	Cephalexin (1st gen cephalosporin) [1]
No improvement 24-48 hrs	A beta-lactamase stable antibiotic:
	Clindamycin or Augmentin (amox/clavulanic acid)
Penicillin allergy	Clindamycin
	Cephalexin (if pen allergy not anaphylactoid type)
	Clarithromycin (Biaxin)[2]
>3 days of symptoms (late)	Clindamycin
	Penicillin VK/metronidazole
	Amoxicillin/metronidazole
Penicillin allergy	Clindamycin

Table 4. Oral Dose Ranges of Antibiotics Useful in Treating Odontogenic Infections[1]

Clinicians must select specific dose and regimen from ranges available to be prescribed based on clinical judgment		
Antibiotic	**Dosage**	
	Children	**Adults**
Penicillin VK	≤12 years: 25-50 mg/kg body weight in equally divided doses q6-8h for at least 7 days; maximum dose: 3 g/day	>12 years: 500 mg q6h for at least 7 days
Clindamycin	8-25 mg/kg in 3-4 equally divided doses	150-450 mg q6h for at least 7 days; maximum dose: 1.8 g/day
Cephalexin (Keflex)	25-50 mg/kg/d in divided doses q6h severe infection: 50-100 mg/kg/d in divided doses q6h; maximum dose: 3 g/24 h	250-1000 mg q6h; maximum dose: 4 g/day
Amoxicillin	<40 kg: 20-40 mg (amoxicillin)/kg/d in divided doses q8h >40 kg: 250-500 mg q8h or 875 mg q12h for at least 7 days; maximum dose 2 g/day	>40 kg: 250-500 mg q8h or 875 mg q12h for at least 7 days; maximum dose: 2 g/day
Amoxicillin/clavulanic acid (Augmentin)	<40 kg: 20-40 mg (amoxicillin)/kg/d in divided doses q8h >40 kg: 250-500 mg q8h or 875 mg q12h for at least 7 days; maximum dose 2 g/day	>40 kg: 250-500 mg q8h or 875 mg q12h for at least 7 days; maximum dose: 2 g/day
MetroNIDAZOLE (Flagyl)		500 mg q6-8h for 7-10 days; maximum dose: 4 g/day

[1]For doses of other antibiotics, see monographs

Penicillin VK p. 62

⌘RX
⌘500 mg tabs # 30
⌘Sig: Tabs 2 stat, then 1 tab 4 times a day for 7 days.

⌘For children, 25-50 mg/kg in divided doses every 6 to 8 hours

Amoxicillin p. 62

⌘Rx
⌘875 mg tabs #20
⌘Sig: One tablet twice daily until gone.

No improvement in 48-72 hours

1. Add metronidazole to the penicillin regimen

OR

2. Discontinue the penicillin and resume therapy with a lactamase-stable AB
   Clindamycin
   Amoxicillin/clavulanic acid (Augmentin)

Adding metronidazole

⌘Metronidazole dose = 500 mg t.i.d. for 7-10 days.
⌘Penicillin VK (or amoxicillin) 500 mg t.i.d. 7-10 days
⌘Note: Bacterial resistance to metronidazole is extremely rare

Clindamycin 300's

⌘Adults: Typical Rx
⌘Clindamycin tabs 300 mg
⌘Disp # 28
⌘Sig: Take one tab 4 times a day for 7 days.

OR – Clindamycin – 150's mg

⌘Adults: Typical Rx
⌘Clindamycin tabs 150 mg
⌘Disp # 56
⌘Sig: Take two tabs 4 times a day for 7 days.

Augmentin (amoxicillin clavulanic acid) p. 62

- ⌘Rx
- ⌘875 mg tabs #14
- ⌘Sig: One tab every 12 hours (morning and bedtime) until gone.

Late Infections-alternate

- ⌘Metronidazole dose = 500 mg t.i.d. for 7-10 days.
- ⌘Penicillin VK (or amoxicillin) 500 mg t.i.d. 7-10 days
- ⌘Note: Bacterial resistance to metronidazole is extremely rare

Antibiotics Used in Dentistry

- ⌘Penicillin VK, Amoxicillin
- ⌘1st generation cephalosporins
  - Keflex; Duricef; Velose
  - 2nd generation cephalosporins
    - cefuroxime
- ⌘Beta-lactamase stable ABs
  - Clindamycin; Augmentin

Cephalexin (Keflex) p. 63

- ⌘RX
- ⌘500 mg tabs # 30
- ⌘Sig: Tabs 2 stat, then 1 tab 4 times a day for 7 days.

- ⌘For children, 25-50 mg/kg per day in divided doses every 6 hours

Cefaclor (Ceclor)

- ⌘RX
- ⌘500 mg tabs
- ⌘Disp #21
- ⌘Sig: One tab 3 times daily.

Z-Pak p. 63

- ⌘Rx
- ⌘Disp #1 pack
- ⌘Sig: Take 2 pills morning of first day, then one pill each morning day 2-5.

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62 10
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Antibiotic-Associated Diarrhea Problem

Two types of diarrhea

1. C. difficile diarrhea (10-20% of all AB-induced diarrhea)

2. Diarrhea from other causes (nuisance diarrhea)

Antibiotic-Associated Diarrhea Problem

Incidence of diarrhea

5-10 % = Pen VK, amoxicillin, ampicillin

10-25% = amoxicillin-clavulanic acid

2-5% = cephalosporins, fluoroquinolones, azithromycin, clarithromycin, erythromycin, tetracylines, clindamycin

Clindamycin and Colitis

- 1. Clindamycin-induced colitis reported in less than1% of medical patients taking daily doses 9 days or more who had no history of colitis
- 2. No reports of a single premedication dose (600 mg) of clindamycin ever causing colitis in pts with no colitis history

Antibiotic-Associated Diarrhea Problem

Nuisance diarrhea – clindamycin, cephalosporins, and amoxicillin-clavulanic acid most frequently associated

ProBiotics

- Give along with the antibiotic to manage diarrhea or prevent diarrhea

Some example products

- Lactinex granules
- Active culture yogart
- Probiotic capsules
- Acidophilus capsules

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Azithromycin (Systemic) (Dental Lexi-Drugs)

(az ith roe MYE sin)

Special Alerts

FDA Issues Warning for Azithromycin Heart Risks

March 2013

The Food and Drug Administration (FDA) has issued a safety warning that azithromycin (Zithromax® or Zmax®) may cause prolonged cardiac repolarization and QT interval, increasing the risk of cardiac arrhythmia and torsade de pointes. Patients at particular risk include those with known risk factors such as existing QT-interval prolongation, a history of torsade de pointes, congenital long QT syndrome, uncompensated heart failure, use of drugs known to prolong the QT interval, uncorrected hypokalemia or hypomagnesemia, or clinically significant bradycardia.

The warning results from FDA review of a research study and a subsequent study conducted by a manufacturer, both assessing the potential for azithromycin to cause abnormal cardiac activity.

Healthcare providers should be aware of the potential for QT-interval prolongation and heart arrhythmias when prescribing or administering azithromycin for patients who are already at risk for cardiovascular events.

Further information may be found at the following websites:

http://www.fda.gov/Drugs/DrugSafety/ucm341822.htm

http://www.fda.gov/Drugs/DrugSafety/ucm304372.htm

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Antibiotic Resistance in Severe Orofacial Infections

E News, LexiComp, Wolters-Kluwer

R.L.Wynn August 25, 2017

Bacterial resistance to antibiotic therapy is an issue in treatment of severe orofacial infections. Antibiotic resistance profile was assessed in patients with severe orofacial infections treated at Massachussetts General Hospital in Boston from 2009 through 2014. Penicillin resistance was found in 32.5% of aerobic isolates and clindamycin resistance was found in 29.3%. *Streptococcus viridans* and *Staphylococcus* species showed increased resistance to clindamycin and erythromycin compared with historic controls.

The authors of the study were from Harvard School of Dental Medicine and Massachusetts General Hospital, Boston. The study can be accessed at: Kim MK, Chuang SK, August M. Antibiotic Resistance in Severe Orofacial Infections. J Oral Maxillofac Surg 2017; 75: 962-968.

Bacterial resistance to commonly used empiric therapy in head and neck infections is frequently reported. Severe orofacial bacterial infections can progress and lead to life-threatening complications including pneumonia, descending mediastinitis, thoracic empyema, pericarditis, septic shock, intraorbital infection, and intracranial spread. Bacterial resistance to antibiotics is a determining factor in progression to these complications. Conventional treatment for these types of infections usually has been high dose penicillins, or clindamycin in patients with penicillin allergy.

Bacterial resistance to penicillin

According to the authors 13% of *Streptococci viridans* cases show resistance to penicillin. This is of some concern since *Streptococci viridans* is the most common isolate in head and neck infections. *Staphylococcus* species are also associated with significant penicillin resistance. *Prevotella* species have been shown to be increasingly resistant to penicillins based on the bacterial production of beta-lactamase enzymes

Bacterial resistance to clindamycin

The authors state that *Streptococcus milleri* resistance to clindamycin has been reported, and clindamycin has minimal efficacy if aerobic gram- negative bacterial are the causative pathogens. They reference studies which report 18% clindamycin resistance in aerobic bacteria and 11% resistance in anaerobic isolates in deep space orofacial infections.

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Newsletter Submitted April 25, 2017

Lexi-Comp

R.L.Wynn

Antibiotic use for prevention of postoperative complications after third molar surgery.

Two studies, addressing the question of whether antibiotics prevent postoperative complications after third molar surgery, find that there is less postoperative complications after using antibiotics.

The first study is:

Lang MS. et al. Do antibiotics decrease the risk of inflammatory complications after third molar removal in community practices? J Oral Maxillofac Surg 2017; 75: 249-255, performed at University of Washington School of Dentistry, Seattle.

Methods Lang et al study

Methods- This was a prospective cohort study which enrolled a sample of patients who had at least one third molar removed in a private practice setting by oral surgeons participating in a practice-based research collaborative from June 2011 through May 2012. The measure was antibiotic use of any type, categorized as yes or no. The primary outcome variable was the presence or absence of an inflammatory complication defined as surgical site infection (SSI) or alveolar osteitis (AO) after third molar removal.

A diagnosis of SSI was made based on visible frank purulence of the traction site at any point postoperatively or unanticipated pain or edema warranting operative intervention or antibiotic use.

A diagnosis of alveolar osteitis was made based on new-onset or increasing pain more than 36 hours after the operation and clinical examination showing loss of blood clot with expose bone, irrigation of the site or gentile probing reproducing the pain, and marked pain relief with application of an anodyne dressing.

A patient-level operative difficulty score (ODS) was created and computed. A score ranging from 0 to 6 was assigned for each third molar removed --- 0= no extraction; 1, nonsurgical erupted; 2, surgical erupted; 3,soft tissue impacted; 4, partial bony impacted; 5, full bony impacted ; 6, complicated or difficult full bony impacted. The score for each third molar removed was summed for a total ODS. For each patient, the ODS could range from 1 (nonsurgical extraction of 1 erupted third molar) to 24 (extraction of 4 difficult full bony impacted third molars.)

Results of the Lang et al study

1. Sample analysis was derived from 105 oral maxilliofacial surgeons who contributed data for 2,954 patients having 9,123 third molars removed. Of the 2,954 patients who had at least one third molar removed, the mean age was 26.4 years and 48% were male.
2. Three fourths of the sample received antibiotics in some form.
3. **Antibiotic group - the overall inflammatory complication frequencies, i.e alveolar osteitis or surgical site infection was 5.0%.**
4. **Non-Antibiotic group - the overall inflammatory complication frequencies, i.e alveolar osteitis or surgical site infection was 7.5%.**
5. **The difference in the inflammatory complication frequencies between the antibiotic group and non-antibiotic group was statistically significant and not by chance.**
6. The mean preoperative disease score was 2.2 (few disease conditions were present) and the mean operative difficulty score was 12.0 (out of a maximum = 24)

"Numbers needed to treat" data interpretation- the authors used the frequency of inflammation data to extrapolate "numbers needed to treat" values. The following were listed

1. Forty patients would need to be treated with antibiotics to prevent 1 postoperative inflammatory complication (SSI or AO).
2. One hundred forty-three patients would need to be treated with antibiotics to prevent 1 surgical site infection.(SSI)
3. Forty patients would need to be treated with antibiotics to prevent one case of alveolar osteitis. (AO)

Antibiotic use

The patterns of antibiotic use were diverse with variations among the type, dose, timing and route of delivery. The specific antibiotics were penicillin, amoxicillin, clindamycin, erythromycin, tetracycline or other. Timing of use included preoperative, intraoperative, postoperative or a combination of exposure times. Delivery routes included oral, parenteral, intra-socket or a combination. An optimum antibiotic use strategy could not be identified.

The Cochrane review report is the second study and is accessed at:

Lodi G et al . **Antibiotics to prevent complications following tooth extractions.** Cochrane Database Syst Rev 2012 Nov 14; DOI: 10.1002/14651858.CD003811.pub2

The objective of the Cochrane study was to determine the effect of antibiotic prophylaxis following tooth extractions. The study searched 5 databases, most going back to 1980, including MEDLINE and the Cochrane Central Register of Controlled Trials. The selection of trials included randomized double-blind placebo-controlled trials of antibiotic prophylaxis in patients undergoing tooth extractions for any indication.

Results

The review included 18 double-blind placebo-controlled trials with a total of 2,456 participants. **Compared to placebo, antibiotics probably reduce the risk of infection in patients undergoing third molar extractions by approximately 70% (rated as moderate quality evidence). This was interpreted as needing 12 people (range 10-17) to be treated with antibiotics to prevent one infection following extraction of impacted wisdom teeth.**

There was evidence that antibiotics may reduce the risk of dry socket by 38% meaning that 38 people would need to take antibiotics to prevent one case of dry socket following extraction of impacted wisdom teeth.

Authors' conclusions

All the trials included in the review included healthy patients undergoing extraction of impacted third molars. It is unclear whether the evidence from this review is applicable to those with concomitant illnesses or immunodeficiency, or those undergoing the extraction of teeth due to severe caries or periodontitis.

Patients at a higher risk of infection are more likely to benefit from prophylactic antibiotics since infections in this group are likely to be more frequent, associated with complications and be more difficult to treat.

One interesting closing message by the authors was the following. "Due to increasing prevalence of bacteria which are resistant to treatment to currently available antibiotics, clinicians should consider carefully whether treating 12 healthy patients with antibiotics to prevent one infection is likely to do more harm than good".

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Pharmacology Update – R Wynn (Spring Study Clubs, 2017)

AAOS Board Approves AUC on Antibiotic Use for Dental Procedures, authored by Terry Stanton and Sheryl Cash. This page may be accessed at

http://www.aaos.org/AAOSNow/2016/Nov/Cover/cover01/?ssopc=1

Accessed Feb 17, 2017 (May have to register to access entire report)

According to the authors, The AAOS began developing Appropriate Use Criteria (AUC) in 2011 as a tool to implement evidence-based clinical practice guidelines. It enabled the clinician to decide on the appropriateness of various treatments in a set of hypothetical, clinically realistic patient scenarios. To date, a list of thirteen orthopedic conditions has been generated in which Appropriate Use Criteria have been established. Among those on the list is "Management of patients with orthopedic implants undergoing dental procedures. This was added as of November 2016. The list of thirteen conditions can be viewed at –

http://www.orthoguidelines.org/go/auc.

Accessed Feb 17, 2017

The authors state that the AUC guidelines relative to the dental antibiotic prophylaxis issue and developed through a collaboration of orthopaedic surgeons, dentists, oral surgeons and epidemiologists recommend that most patients are not at risk for infection following dental procedures and do not require antibiotic administration. However, antibiotic therapy should be considered for certain subsets of patients, primarily those with the following conditions:

- Severely compromised immune systems related to AIDS/HIV,
- Uncontrolled diabetes
- Chemotherapy
- Recent history of joint infection
- Taking certain drugs for rheumatoid arthritis or to prevent organ transplant complications

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17 58

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AAOS Introduces the "AUC APP"

The AUC app, available through the AAOS OrthoGuidelines website,

http://www.orthoguidelines.org/go/auc/default.cfm?auc_id=224995&actionxm=Terms

can be accessed at the above site. On this site, scroll to bottom to click "I have read and understand the assumptions and disclaimer". This will then open the AUC app.

The app uses input from the dental professional to gauge risk related to the overall health of the patient, the timing since joint replacement and the type of dental procedure to be performed. The app has 64 scenarios with each having an antibiotic "appropriateness rating: from 1 to 9, as determined by the 14 member voting panel of orthopaedic surgeons, oral surgeons, dentists and epidemiologists. The rating 1 to 3 indicates that antibiotic use is "rarely appropriate"; 4to 6 means that antibiotics "may be appropriate"; rating between 7 and 9 means that antibiotic use is "appropriate for the indication provided and is likely to improve health outcomes or survival"

The app provides the following fields and criteria within the fields as shown below.

Planned dental procedure

-Dental procedures that do not result in the manipulation of periapical tisues, or perforation of the oral mucosa

-Dental procedures that involve manipulation of periapical tissues, or perforation of the oral mucosa

Immunocompromised Status

-Not severely immunocompromised

-Severely immunocompromised

Diabetic Glycemic Control

-No current or active diabetes diagnosis

-Active known diabetic, Hemoglobin A1c < 8 or Blood Glucose < 200

-Active known diabetic, Hemoglobin A1c $\geq$ 8 or Blood Glucose $\geq$200

-Active known diabetic, Hemoglobin A1c Unknown, Blood Glucose unknown

History of periprosthetic or deep prosthetic joint infection that required an operation

-No history of periprosthetic or deep prosthetic infection that required an operation

-History of periprosthetic or deep prosthetic infection that required an operation that required operation

Timing since joint replacement procedure

-Less than 1 year

-1 year or longer

45

45

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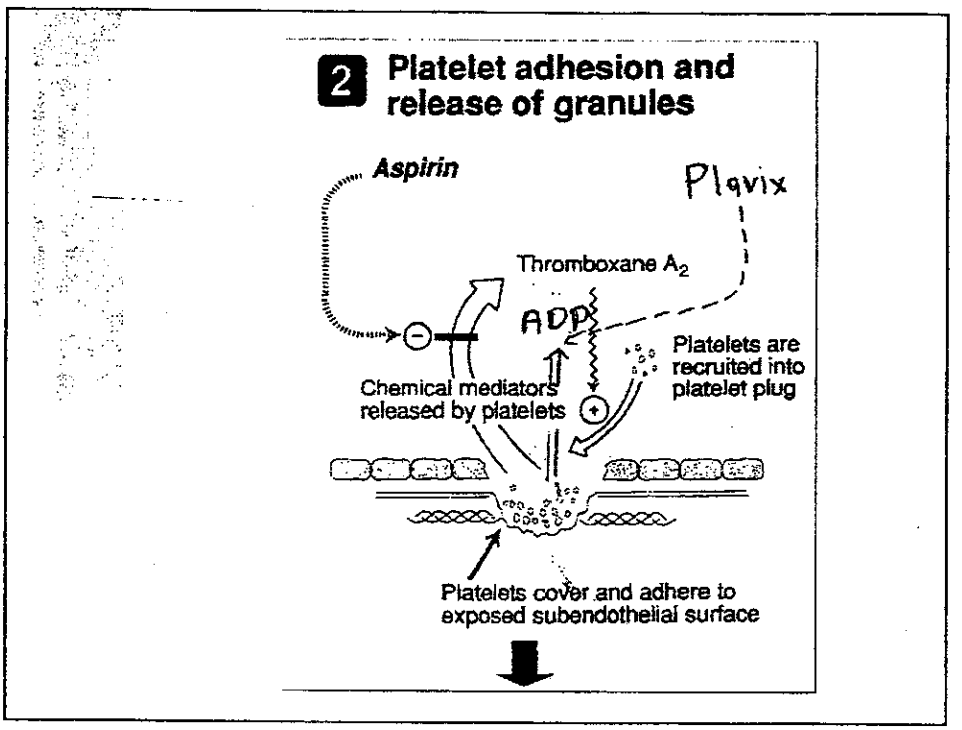
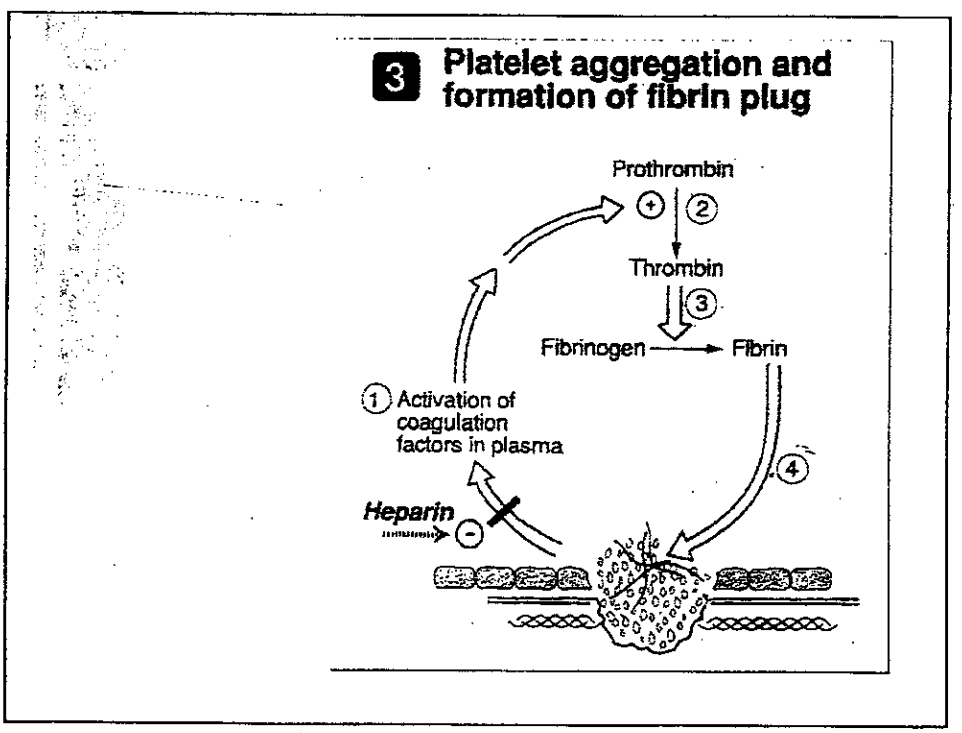
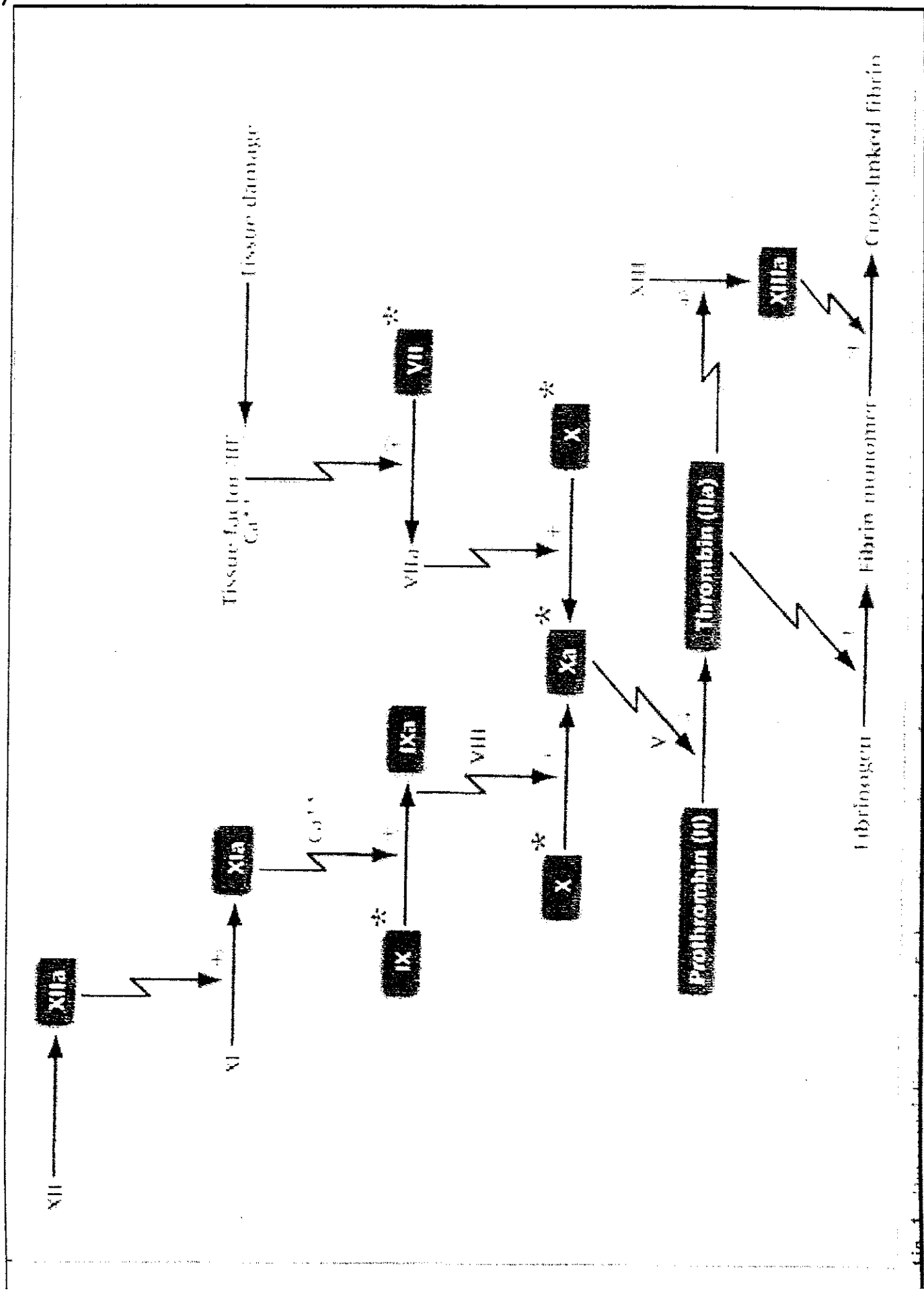

2 Platelet adhesion and release of granules
Aspirin
Plavix
Thromboxane A_2
ADP
Platelets are recruited into platelet plug
Chemical mediators released by platelets
Platelets cover and adhere to exposed subendothelial surface


3 Platelet aggregation and formation of fibrin plug
Prothrombin
2
Thrombin
3
Fibrinogen
Fibrin
1 Activation of coagulation factors in plasma
4
Heparin


XII
XIIa
XI
XIa
IX
IXa
VIII
X
Xa
Prothrombin (II)
Thrombin (IIa)
V
Fibrinogen
Fibrin monomer
XIII
XIIIa
Cross-linked fibrin
Tissue factor (TF)
VII
VIIa
X
Tissue damage

Secondary Prevention – had a previous cardiac event

- Aspirin 75-162 mg daily in all patients with coronary artery disease unless contraindicated
- American Heart Assoc recs 2011

ASA for Primary Prevention 75-162mg/day

- **1.** If you are in your 50's, have a 10% or greater risk of heart attack over next 10 years, have a life expectancy of at least 10 years, and do not have risk of GI bleeding
- American Heart Assoc 2016
- www.cvriskcalculator.com

ASA for Primary Prevention 75-162mg/day

- **2.** If you are in your 60's, have a high risk of having a heart attack or stroke over next 10 years and have life expectancy of at least 10 years, and do not have increased risk of GI bleeding
- American Heart Assoc 2016
- www.cvriskcalculator.com

ASA for Primary Prevention – evidence insufficient

- Younger than 50 yrs or older than 70 years, there is insufficient evidence of aspirin benefits.
- Please consult with your doctor

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Oral Anticoagulant p 47

- Warfarin (Coumadin)

Warfarin (Coumadin)

- Used in atrial fib patients
- CAD patients
- MI survivors
- Other coronary heart disease conditions

Used to Prevent Deep Vein Thrombosis (DVT)

- DVT – serious and potentially fatal
- Affects 2 out of 1000 individs per year
- Classic risk factors = immobilizaton, CA, fractures, HRT, pregnancy, childbirth, surgery
- Most recent = assoc between atherosclerotic disease and spont DVT. Atherosclerotic disease may induce DVT. NEJM 2003; 348:15

If nec - Coumadin dose can be reduced prior to dental surgery

- Typical Coumadin patient will be dosed to achieve INR 2.5 to 3.5 values
- In many cases, when INR is 3.0 or less, no dose adjustment nec
- If over 3.0 – 3.5, doc could adjust dose day prior to surgery, dose could be reduced in order to achieve INR value less than 2.5
- After surgery, physician will re-establish Coumadin dosing

INR reference

- INR international normalized ratio
- 1
- 2
- 3
- 4
-

- Prothrombin times
- 12 secs
- 23 secs
- 32 secs
- 44 secs
- So on

Warfarin (Coumadin)

- Requires repeated monitoring for --
  - – INR values for dose adjustment
  - – Dietary vitamin K levels and dietary adjustment

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Oral Antiplatelet Comparison Chart

Medication	Mechanism of Action	Reversible Platelet Inhibition	Prodrug	Metabolism	Pharmacotherapy Pearls
Aspirin	Inhibits cyclooxygenase-1 and 2	No	No	CYP2C9	Chronic NSAID use can compromise antiplatelet effects Monitor for GI ulceration
Cilostazol (Pletal)	Inhibits platelet phosphodiesterase III	Yes	No	CYP3A4 CYP2C19 CYP1A2 CYP2D6	Administer before or 2 hours after meals Contraindicated in patients with heart failure of any severity CYP3A4 and 2C19 drug interactions
Clopidogrel (Plavix)	Inhibits $P2Y_{12}$ component of ADP receptors	No	Yes	CYP2C19 CYP3A4	CYP2C19 inhibitors may reduce concentrations of active metabolite CYP2C19 polymorphisms may affect clopidogrel efficacy
Prasugrel (Effient)	Inhibits $P2Y_{12}$ component of ADP receptors	No	Yes	CYP3A4 CYP2B6	Reduce maintenance dose to 5 mg in patients <60 kg Contraindicated in patients with history of stroke, TIA Not recommended in patients ≥75 years of age

Medication	Mechanism of Action	Reversible Platelet Inhibition	Prodrug	Metabolism	Pharmacotherapy Pearls
Ticagrelor (Brilinta)	Inhibits $P2Y_{12}$ component of ADP receptors	Yes	No	CYP3A4 CYP3A5	Used in combination with aspirin; daily maintenance aspirin dose should not exceed 81 mg CYP3A4 drug interactions BID dosing Monitor closely for dyspnea, bradyarrhythmia (including ventricular pauses)
Ticlopidine	Inhibits $P2Y_{12}$ component of ADP receptors	No	Yes	CYP3A4	Black Box warning on hematologic toxicities (aplastic anemia, TTP) Frequent CBC monitoring required BID dosing
Vorapaxar	Inhibits PAR-1	Yes[3]	No	CYP3A4 CYP2J2	Use in combination with aspirin and/or clopidogrel Contraindicated in patients with history of stroke, TIA, or ICH Extremely long effective half-life of 3 to 5 days

[1]Management of antiplatelet-associated bleeding requires careful consideration of the indication for antiplatelet extent (eg, epistaxis vs intracranial hemorrhage); minor bleeding may only require local hemostasis.

[2]When urgent CABG is necessary, the ACCF/AHA CABG guidelines recommend discontinuation for at least 24 (Hillis 2011).

[3]Due to the very long half-life, vorapaxar is effectively irreversible.

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Oral Anticoagulant Comparison Chart

Medication	Mechanism of Action	Metabolism	Monitoring Parameters	Pharmacotherapy Pearls
Warfarin	Inhibits formation of vitamin K-dependent clotting factors II, VII, IX, X, and proteins C and S	CYP2C9 CYP1A2 CYP3A4 CYP2C19	PT/INR (individualized; depends on INR stability)	CYP1A2, 3A4, 2C9, and 2C19 drug interactions and vitamin K-containing food interactions Full therapeutic effect usually seen within 5 to 7 days Half-life is ~40 hours
Dabigatran (Pradaxa)	Directly inhibits thrombin	Hepatic glucuronidation P-gp substrate	Routine lab monitoring not required; aPTT, ECT (if available), TT (most sensitive) may be used to detect presence of dabigatran Renal function	Compliance issues (BID dosing) Specific conversions to/from warfarin, parenteral anticoagulants Renal dosing adjustment required; per ACCP, contraindicated with CrCl ≤30 mL/minute Use with caution in patients ≥80 years of age Dose reduction or avoidance required if used with dronedarone, ketoconazole, P-gp inhibitors P-gp drug interactions Half-life is 12 to 17 hours; considerably prolonged with severe renal impairment

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Medication	Mechanism of Action	Metabolism	Monitoring Parameters	Pharmacotherapy Pearls
Edoxaban (Savaysa)	Directly inhibits factor Xa	CYP3A4 (minor) Hydrolysis (minimal)	Routine lab monitoring not required	Specific conversions to/from warfarin, parenteral anticoagulants
		P-gp substrate		DVT/PE: Dose reduction necessary for patients <60 kg, concomitant P-gp inhibitor, or if CrCl 15 to 50 mL/min. Not recommended if CrCl <15 mL/min NVAF: **Do not use if CrCl >95 mL/min.** Dose reduction necessary if CrCl 15 to 50 mL/min. Not recommended if CrCl <15 mL/min
Rivaroxaban (Xarelto)	Directly inhibits factor Xa	CYP3A4 CYP3A5 CYP2J2 P-gp substrate	Routine lab monitoring not required; may use PT to detect presence of rivaroxaban Renal and hepatic function	Administer doses ≥15 mg/day with food Dosing frequency depends on indication Specific conversions to/from warfarin, parenteral anticoagulants Renal dosing adjustment required Avoid in moderate or severe hepatic impairment CYP3A4 and P-gp drug interactions Half-life is 5 to 9 hours; slightly prolonged with renal impairment

Medication	Mechanism of Action	Metabolism	Monitoring Parameters	Pharmacotherapy Pearls	F
Apixaban (Eliquis)	Directly inhibits factor Xa	CYP3A4 P-gp substrate	Routine lab monitoring not required; PT, INR, and aPTT may be used to detect presence of apixaban	Compliance issues (BID dosing) Specific conversions to/from warfarin, parenteral anticoagulants Renal dosing adjustment required (NVAF); the AHA/ASA recommends to avoid use with CrCl <25 mL/minute Not recommended in patients with severe liver impairment CYP3A4 and P-gp drug interactions Half-life is ~8 to 15 hours; slightly prolonged with renal impairment	

Abbreviations: ACCP = American College of Chest Physicians, AHA/ASA = American Heart Association/Ameri Association, aPTT = activated partial thromboplastin time, BID = twice daily, DVT = deep venous thrombosis, E time, FFP = fresh frozen plasma, INR = international normalized ratio, NVAF = nonvalvular atrial fibrillation, PC complex concentrate, PE = pulmonary embolism, P-gp = P-glycoprotein, PT = prothrombin time, TT = thrombin

lating dabigatran will inhibit any newly transfused thrombin. Recombinant factor VIIa (rFVIIa) is a potent procoagulant and general haemostatic agent that can initiate haemostasis at sites of bleeding by directly activating thrombin on the surface of platelets

mencing the dabigatran is easier and causes less risk than warfarin. These decisions should still only be made in conjunction with the patient's general medical practitioner. The protocol recommends not stopping the dabigatran for standard procedures such as

Table 4. Summary of management of oral surgical patients taking dabigatran

	Guidelines
Dental procedures and uncomplicated simple tooth extractions	- Not necessary to discontinue use of dabigatran in patients with normal renal function - Local haemostatic measures need to be applied – mechanical pressure, suturing and local haemostats
Extraction of multiple teeth or elective oral/maxillofacial surgical procedures or patients taking other anticoagulants or antiplatelet agents	- Consider referral to an oral and maxillofacial surgeon - In consultation with the patient's physician, will consider discontinuing dabigatran or changing to another anticoagulant preoperatively - If normal renal function will discontinue dabigatran 24 hours before procedure - Consider checking aPTT preop - If abnormal renal function, consider discontinuing for 48 hours or longer depending on degree of renal impairment[16] - Local haemostatic measures should be used - Can recommence dabigatran 24–48 hours after operation
Emergency oral/maxillofacial surgical procedures or patients presenting with severe haemorrhage	- Refer immediately to a tertiary referral centre - Cease dabigatran, mechanical pressure, maintain intravascular volume with fluid resuscitation and blood products such as FFP - Contact haematology for consideration of rFactor VIIa administration or other agents - Consider haemodialysis

Nitrous Oxide (Dental Lexi-Drugs) FDA Monograph

Pharmacologic Category

Dental Gases; General Anesthetic

Dental Use

Induction of sedation and analgesia in anxious dental patients

Use

, analgesia, and amnesia; principal adjunct to inhalation and intravenous general anesthesia

Local Anesthetic/Vasoconstrictor Precautions

No information available to require special precautions

Effects on Dental Treatment

No significant effects or complications reported

Effects on Bleeding

No information available to require special precautions

Adverse Reactions

Frequency not defined.

Cardiovascular: Hypotension

Central nervous system: Central nervous system stimulation, confusion, dizziness, headache

Gastrointestinal: Nausea and vomiting

Respiratory: Apnea

Dental Usual Dosage

Sedation and analgesia: Children and Adults: Concentrations of 25% to 50% nitrous oxide with oxygen

Dosing: Adult

Surgical sedation and analgesia: Concentrations of 25% to 50% nitrous oxide with oxygen. For general anesthesia, concentrations of 40% to 70% via mask or endotracheal tube. Minimal alveolar concentration (MAC), which can be considered the ED_{50} of inhalational anesthetics, is 105%; therefore delivery in a hyperbaric chamber is necessary to use as a complete anesthetic. When administered at 70%, reduces the MAC of other anesthetics by half.

Dental: Sedation and analgesia: Concentrations of 25% to 50% nitrous oxide with oxygen

Dosing: Geriatric

Refer to adult dosing.

Dosing: Pediatric

Refer to adult dosing.

Mechanism of Action

General CNS depressant action; may act similarly as inhalant general anesthetics by stabilizing axonal membranes to partially inhibit action potentials leading to sedation; may partially act on opiate receptor systems to cause mild analgesia; central sympathetic stimulating action supports blood pressure, systemic

vascular resistance, and cardiac output; it does not depress carbon dioxide drive to breath. Nitrous oxide increases cerebral blood flow and intracranial pressure while decreasing hepatic and renal blood flow; has analgesic action similar to morphine.

Contraindications

Hypersensitivity to nitrous oxide or any component of the formulation; nitrous oxide should not be administered without oxygen

Use is considered contraindicated in patients having undergone vitreoretinal surgery and presence of intraocular gas bubble (Lee, 2004; Fu, 2002).

Warnings/Precautions

Concerns related to adverse effects:

- Addictive: May be associated with abuse and/or addiction.
- Body space volume expansion: Both compliant (eg, bowel gas, pneumothorax) and poorly compliant (eg, middle ear) body spaces may be prone to changes in volume due to nitrous oxide transfer; avoid use in pneumothorax, pneumocephalus, middle ear surgery, or bowel obstruction (Miller 2010; Ohryn 1995; Sprehn 1992).
- Bone marrow suppression: Prolonged use may produce bone marrow suppression; patients with vitamin B_{12} deficiency (pernicious anemia) and those with other nutritional deficiencies (alcoholics) are at increased risk.
- Nausea/vomiting: Occurs postoperatively in ~15% of patients.
- Neurologic effects: Prolonged use may produce neurologic dysfunction; patients with vitamin B_{12} deficiency (pernicious anemia) and those with other nutritional deficiencies (alcoholics) are at increased risk.

Disease-related concerns:

- Vitreoretinal surgery: Detached retina and other ocular disorders treated with vitreoretinal surgery where intraocular gas was used: Nitrous oxide can increase intraocular pressure which may result in retinal artery occlusion, ischemia, or optic nerve damage and vision loss in these patients. Nitrous oxide should not be used in patients who have had an intravitreal gas bubble unless it can be confirmed that the bubble has been completely resorbed (Fu, 2002; Lee, 2004).

Other warnings/precautions:

- Oxygen use: Oxygen should be briefly administered during emergence from prolonged anesthesia with nitrous oxide to prevent diffusion hypoxia.

Metabolism/Transport Effects

None known.

Drug Interactions

Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr in adults when used with other CNS depressants. *Risk D: Consider therapy modification*

Cannabis: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

HYDROcodone: CNS Depressants may enhance the CNS depressant effect of HYDROcodone. Management: Avoid concomitant use of hydrocodone and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*

Opioid Analgesics: CNS Depressants may enhance the CNS depressant effect of Opioid Analgesics. Management: Avoid concomitant use of opioid analgesics and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*

OxyCODONE: CNS Depressants may enhance the CNS depressant effect of OxyCODONE. Management: Avoid concomitant use of oxycodone and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: CNS Depressants may enhance the adverse/toxic effect of Selective Serotonin Reuptake Inhibitors. Specifically, the risk of psychomotor impairment may be enhanced. *Risk C: Monitor therapy*

Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem adult dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. *Risk D: Consider therapy modification*

Onset of Action

Inhalation: 2-5 minutes

Absorption

Rapidly via lungs; blood/gas partition coefficient is 0.47

Metabolism

Body: <0.004%

Excretion

Primarily exhaled gases; skin (minimal amounts)

Pregnancy Considerations

Nitrous oxide crosses the placenta in concentrations ~80% of those in the maternal plasma. The half-life in the neonate is ~3 minutes and it is quickly eliminated from neonatal lungs with the onset of breathing (Rooks, 2011). Infertility, spontaneous abortion, and congenital abnormalities have been reported following prolonged occupational exposure (Becker, 2008; Brodsky, 1986; Rooks, 2011). Adverse events are related to dose and duration of exposure and risks may be decreased with proper administration procedures (Rooks, 2011). May be used when needed for dental treatments that cannot be postponed during pregnancy; use for labor analgesia is considered acceptable (Becker, 2008; Rooks, 2011). Avoid use in pregnant women during the first two trimesters of pregnancy, those with medical conditions that increase the risk of vitamin B_{12} deficiency, or infertile women undergoing *in vitro* fertilization (Brodsky, 1986; Rooks, 2011).

Dosage Forms

Supplied in blue cylinders

Trace anesthetics and long term exposure – nitrous oxide

⌘1. 1970's reported a link between spontaneous miscarriages to anesthetic exposure in OR nurses and female anesthetists. No specific agent incriminated but nitrous was suspicious

⌘2. 1975 – association between exposures to halothane-nitrous oxide and spontaneous abortions.

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Trace anesthetics and long term exposure – nitrous oxide

⌘3. Exposure levels associated with spontaneous abortions between 500 and 6,000 ppm for over 3 hours per week.

⌘4. Studies criticized because they were rertrospective and frought with other possibilities of cause such as emotional and physical rigors of presence in OR.

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Trace anesthetics and long term exposure – nitrous oxide

⌘5. 1980 – Mail survey of over 30,000 dentists and 30,000 chairside assistants exposed to trace anesthetics in dental settings

⌘Long term exposure to nitrous oxide led to increase in general health problems and reproductive difficulties

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Trace anesthetics and long term exposure – nitrous oxide

⌘6. 1986 - Study reported four female dental personnel exposed to inhalation-sedation techniques with 35% nitrous oxide reported 6 spontaneous abortion out of 7 pregnancies during a 17 month period.

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Trace anesthetics and long term exposure – nitrous oxide

⌘7. Rowland study on decrease in fertility associated with nitrous oxide-questionnaire to 7000 female dental personnel

⌘A.Exposure to nitrous oxide for more than 5 hours a week were less fertile than women unexposed

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Trace anesthetics and long term exposure – nitrous oxide

⌘B. The exposed women (greater than 500 ppm 5 hours per week or more) were only 41% as likely as unexposed women to conceive during each monthly cycle.

⌘C. No indication of reduced fertility in women exposed to "scavenged" nitrous oxide more than 5 hours per week, or "unscavenged" less than 5 hours per week.

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NITROUS OXIDE: A REVIEW

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LEARNING OBJECTIVES

After reading this article, the dentist will be able to:

- list three indications and two contraindications for the use of nitrous oxide in dentistry.
- list two pharmacological effects that make nitrous oxide useful in dentistry.
- describe the use of nitrous oxide in medicine.
- list the nitrous oxide dosage required to produce sedation and analgesia.
- describe how nitrous oxide may work at the cellular level to produce sedation and analgesia.
- explain the rapid pharmacokinetic onset of nitrous oxide.
- define diffusion hypoxia and its results.
- describe cardio-respiratory effects associated with clinical concentrations of nitrous oxide.
- describe how nitrous oxide causes nausea and vomiting.
- name some commercial sources of nitrous oxide that lead to abuse.
- describe the effect of nitrous oxide on fertility and spontaneous abortion in female dental personnel in operatories using unscavenged gases.

INTRODUCTION

Nitrous oxide sedation in dental practice is a condition of reduced pain perception and sedation without the loss of consciousness, leaving vital reflexes intact. Today, nitrous oxide is used in combination with oxygen, but for simplicity it is referred to in this article as nitrous oxide rather than nitrous oxide/oxygen. Nitrous oxide is an important adjunct to pain control together with local anesthesia, a combination called "relative analgesia." When used correctly,

nitrous oxide has valuable sedative and anti-anxiety abilities and is very suitable for the anxious patient undergoing painful dental treatment. Ease of administration, few contraindications, and a high degree of safety have made nitrous oxide sedation very popular among patients and dentists.

The standard indications for nitrous oxide in dentistry are: anxiety, painful treatment, and increased pharyngeal reflex activity. Contraindications are: nasal obstruction (stuffiness) and pregnancy (1st trimester). Nitrous oxide should be administered with care to patients with severe cardiovascular and respiratory disease and severe psychiatric problems.

The greatest benefit of nitrous oxide in dentistry is that it minimizes patient apprehension and fear. Analgesia is also provided in concentrations of 15 to 45%, which also alters the patient's reaction to "dental pain." In these concentrations, nitrous oxide produces quantifiable, statistically significant, and subjectively meaningful increases in the thresholds of pain and pain tolerance. Controlled clinical studies[1] have confirmed that low doses of nitrous oxide produces significant analgesia as well as sedation. It has been estimated that nitrous oxide as a sedative and analgesic agent is used by over 35% of all practicing dentists in the U.S.[2]

Nitrous oxide is used in medicine as an adjunct to general anesthesia. It has low potency as a general anesthetic and low muscle relaxant properties. Its minimum alveolar concentration (MAC) is greater than 100 vols %, which is the clinical potency of nitrous oxide compared to other general anesthetic agents. The MAC is defined as the minimum alveolar concentration necessary to prevent movement in 50% of the people subjected to painful stimulus, such as skin incision. Comparative MACs for volatile liquids used as general anesthetics are: halothane 0.8, enflurane 1.7, isoflurane 1.2, and methoxyflurane 0.2. The volatile anesthetics are usually administered with nitrous oxide (up to 70 vols %) to reduce the quantity of volatile agent required to maintain general anesthesia in patients undergoing surgery.

Dose

The dose of nitrous oxide to produce sedation and analgesia is 25 to 50% in a mixture of oxygen. Administration of nitrous oxide in a concentration of 25% in oxygen, in combination with local anesthesia, was evaluated as a sedative in 394 dental patients suffering anxiety. Ninety-nine percent of these patients were successfully treated without loss of consciousness, including 47 children (88 occasions).[3] Continuous inhalation of nitrous oxide 30%/oxygen 70% was an effective analgesic in children presenting to an emergency room with mild lacerations.[4] In this study, pain perception was diminished with the use of the nitrous oxide mixture in children more than eight years of age. Although a trend toward a decrease in pain perception was observed in younger patients (two to seven years), this effect was not significant. Adverse effects were not observed during administration of 30% nitrous oxide. The use of higher concentrations of nitrous oxide (40% to 50%) may produce greater analgesia.[4]

Physical Properties

Nitrous oxide is a colorless, heavier-than-air gas without appreciable odor or taste. It is the only inorganic gas that is practical for use in general anesthesia. It is marketed in steel cylinders as a colorless liquid under pressure in equilibrium with its gas phase. As it is released from the cylinder, some of the liquid nitrous oxide returns to the gaseous state; the pressure in the tank thus remains nearly constant until all the liquid has evaporated. The heat required for its vaporization is obtained from the walls of the cylinder and surrounding air, with the result that the tank becomes cold. Although the gas is not flammable, it supports combustion as actively as oxygen does when it is in proper concentration with a flammable anesthetic.

History and Development

In 1798, English scientist Humphrey Davy first noted that nitrous oxide had an analgesic effect on toothache.[5] Later use of nitrous oxide as an analgesic