

## **Introduction:**

Considering the vast amount of information and literature pertaining to the field of endodontics, one of the most important sources for both oral and written board exams such as *basic sciences (anatomy, physiology), management of medically compromised patients and drug interactions* can be easily overlooked. The present study guide encompasses basic sciences behind the field of endodontics. By compiling the important concepts adopted from Pathway of the Pulp text book (Eleventh edition), this study guide will help residents and board candidates to focus on many questions regarding basic science in a short amount of time. Also, heavy emphasis was placed on the management of medically compromised patients and drug interactions. This has been the main field of interest for both oral and written board exams. This part has been exactly adopted from “Little and Falace's Dental Management of the Medically Compromised Patient”. Not only are dental management charts included but also pathophysiology and possible drug interactions have been summarized for easier access and better understanding. We acknowledge the work that has been done to put the above-mentioned resources together and hope residents and board candidates will find this guide helpful as they prepare for the process of board certification.

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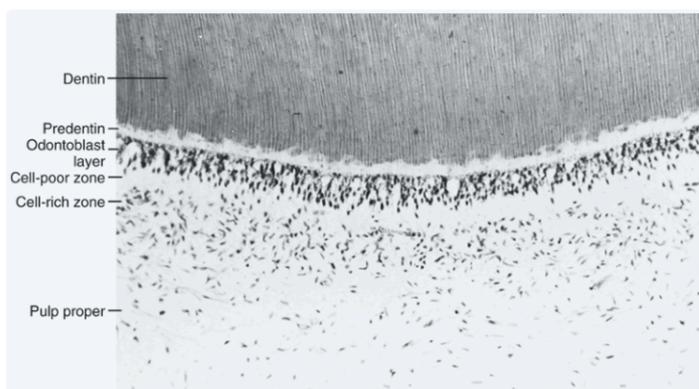
## Structure and function of dentin-pulp complex:

### **Dentin structure:**

Many characteristics of the tubules are important to the structural behavior of dentin, its permeability, and in achieving strong adhesive bonds. Of primary importance are the tubule density, tubule diameter, and spatial variations in these measurements. In the crown, the average density ranges from approximately 15,000 to 65,000 tubules per  $\text{mm}^2$ . The tubule diameter decreases from approximately  $2.5 \mu\text{m}$  (near the pulp) to less than  $1 \mu\text{m}$  at the DEJ. The mean density ranged from approximately 8,000 to 58,000 tubules/ $\text{mm}^2$  and the crown exhibited significantly greater tubule density than the root. Radicular dentin exhibited larger diameter tubules than the crown, but had a lower density. Indeed, Komabayashi et al. reported a density of 14,000 to 32,000 tubules/ $\text{mm}^2$  1–2 mm below the cemento–enamel junction of human canines, which is much lower than equivalent measures in the crown; the density effectively doubled from the outer wall (near the periodontal ligament) to the region adjacent to the pulp (Endodontic topics Dwayne Arola, Microstructure and mechanical behavior of radicular and coronal dentin ).

### **Pulp-dentin complex (Pathways, ch.12):**

The outermost stratum of cells of the healthy pulp is the odontoblast layer. This layer is located immediately subjacent to the predentin. The odontoblast processes, however, pass on through the predentin into the inner part of dentin. Consequently, the odontoblast layer is actually composed of the cell bodies of odontoblasts. In addition, capillaries, nerve fibers, and dendritic cells may be found among the odontoblasts. Immediately subjacent to the odontoblast layer in the coronal pulp, there is often a narrow that is relatively free of cells and hence is called the *cell-free layer of Weil*. It is traversed by blood capillaries, unmyelinated nerve fibers. Besides fibroblasts, the cell-rich zone may include a variable number of immune cells like macrophages and dendritic cells, but also undifferentiated mesenchymal stem cells.



## **Pulp ground substance (Pathways, ch.12):**

The major structural component of the interstitium is collagen. The network of collagen fibers also supports the other components of the interstitium, the proteoglycans, hyaluronan, and elastic fibers. The two former components represent the glycosaminoglycans of the interstitial matrix. Because of its content of polyanionic polysaccharides, the interstitium is responsible for the water-holding properties of connective tissues and acts as a molecular sieve in regulating the diffusion of substances through this space. Nearly all proteins of the ECM are glycoproteins. Proteoglycans are an important subclass of glycoproteins. These molecules support cells, provide tissue turgor, and mediate a variety of cell interactions. They have in common the presence of GAG chains and a protein core to which the chains are linked. Except for heparan sulfate and heparin, the chains are composed of disaccharides. The primary function of GAG chains is to act as adhesive molecules that can bond to cell surfaces and other matrix molecules.

Proteoglycans can regulate the dispersion of interstitial matrix solutes, colloids, and water, and (in large measure) they determine the physical characteristics of a tissue, such as the pulp. GAGs are unique in the way that they bind to  $Ca^{+}$ . One of the main GAG is chondroitin sulfate that play a major role in tissue development. Fibronectin is a major surface glycoprotein that, together with collagen, forms an integrated fibrillary network that influences adhesion, motility, growth, and differentiation of cells. Laminin, an important component of basement membranes, binds to type IV collagen and cell surface receptors. Tenascin is another substrate adhesion glycoprotein. In the pulp, the principal proteoglycans include hyaluronic acid dermatan sulfate, heparan sulfate, and chondroitin sulfate. The proteoglycan content of pulp tissue decreases approximately 50% with tooth eruption. During active dentinogenesis, chondroitin sulfate is the principal proteoglycan, particularly in the odontoblast and predentin layer, where it is somehow involved with mineralization; with tooth eruption, hyaluronic acid and dermatan sulfate increase, and chondroitin sulfate decreases greatly.

\*Fibronectin is a major surface glycoprotein that, together with collagen, forms an integrated fibrillary network that influences adhesion, motility, growth, and differentiation of cells. Laminin, an important component of basement membranes, binds to type IV collagen and cell surface receptors. Tenascin is another substrate adhesion glycoprotein.

\*Type I and type III collagen represent the major subtypes of collagen in the pulp, and type I is found in thick striated fibrils throughout the pulp tissue

Type I collagen is found in skin, tendon, bone, dentin, and pulp.

Type II collagen is found in cartilage.

Type III collagen is found in most unmineralized connective tissues. It is a fetal form found in the dental papilla and the mature pulp. In bovine pulp, it constitutes 45% of the total pulp collagen during all stages of development.

Types IV and VII collagen are components of basement membranes.

Type V collagen is a constituent of interstitial tissues.

Type VI collagen is a heterotrimer of three distinct chains, alpha 2 (VI) and alpha 3 (VI), and is widely distributed in low concentrations in soft tissues at interfibrillar filaments.

Type I collagen is synthesized by odontoblasts and osteoblasts; fibroblasts synthesize types I, III, V, and VII collagen.

### **Innervation of the pulp, trigeminothalamic pathway (Pathways, ch.12, 17):**

\* Direct actions of odontoblasts on dental nerves and vice versa have been proposed based on the excitability of odontoblasts, the differential expression of receptors for neuropeptides on odontoblasts, the demonstration of the thermosensitive transient receptor potential (TRP) ion channels, and the finding that all nine voltage-gated sodium channels are variably expressed on odontoblasts in developing, mature, and aging rat teeth. In addition, a possible function of odontoblast in immune regulation has been proposed by the finding of innate immune components in the odontoblast layer.

The innervation of the pulp includes both afferent neurons, which conduct sensory impulses, and autonomic or efferent neurons, which provide neurogenic modulation of the microcirculation, inflammatory reactions, and perhaps regulate dentinogenesis.

In the peripheral nervous system, these neurons or nerves are referred to as primary afferent (i.e., sensory) fibers. The primary afferent fibers can broadly be divided into A-beta fibers, which transmit light touch or proprioceptive information, and A-delta and C fibers, which encode pain. The tooth is densely innervated by afferent nerve fibers, which are believed to transmit mainly pain in response to thermal, mechanical, or chemical stimuli. The majority of dental nerves are C fibers that innervate the central pulp, most of which terminate beneath the odontoblasts.

**A-beta Fibers:** The rapidly conducting myelinated neurons that respond to light touch are called A-beta fibers. Under normal conditions, activation of the A-beta fibers by high-intensity stimulation results in low-frequency output in the central nervous system. Activation of A-beta fibers normally is interpreted as non-painful mechanical stimulation or, under certain conditions, can be perceived as a “pre-pain” sensation. A-beta fibers also have been shown to undergo phenotypic changes that allow them to encode painful stimuli under certain inflammatory conditions.

**A-delta Fibers:** The A-delta fibers are lightly myelinated, have a faster conduction velocity than C fibers, and are believed to transmit a sharp or pricking sensation. A-delta fibers respond primarily to noxious mechanical stimuli rather than to chemical or thermal stimuli. Other A-delta fibers may be polymodal (responding to mechanical, chemical, and thermal stimuli) or respond only to cold/mechanical or hot/mechanical noxious stimuli. In the tooth pulp, A-delta fibers traverse the odontoblastic layer and terminate in the dentinal tubules. Because of their location and their sensitivity to mechanical stimulation, A-delta fibers are believed to respond

to stimuli that result in movement of fluid within the dentinal tubules (e.g., osmotic, mechanical probing, or thermal stimuli applied to the external surface of the tooth). Consistent with the hypothesized mechanism of dentinal pain is the fact that the stimuli that cause dentinal fluid movement result in a sharp pain associated with A-delta fiber activation. When intense noxious stimuli activate the A-delta fibers, the input to the central nervous system consists of high-frequency action potentials.

**C Fibers:** The C fibers are unmyelinated, have slower conduction velocity, and are associated with a dull, aching, or burning sensation. Most C fibers are polymodal, responding to mechanical, thermal, and chemical stimuli. Because of the difference in conduction velocities, A-delta fibers are believed to transmit early, shooting pain, whereas C fibers would transmit late, dull pain and vibration. Noxious stimuli that exceed the receptor threshold of these nociceptive primary afferent terminals result in action potentials that travel centrally, signaling tissue damage. In the pulp tissue, the more centrally located C fibers respond to thermal, mechanical, and chemical stimuli and are believed to be sensitized by inflammation. All visceral structures are innervated primarily by afferent fibers conducting nociceptive information such as that carried by A-delta and C fibers.

\* In the human premolar, the number of unmyelinated axons entering the tooth at the apex reached a maximal number shortly after tooth eruption. At this stage, an average of 1800 unmyelinated axons and more than 400 myelinated axons were found, although in some teeth fewer than 100 myelinated axons were present. Five years after eruption, the number of A fibers gradually increased to more than 700. The relatively late appearance of A fibers in the pulp may help to explain why the electric pulp test tends to be unreliable in young teeth, as A fibers are more easily electrically stimulated than C fibers. Overall, approximately 80% of the axons were unmyelinated fibers and there are three to eight times more unmyelinated C fibers than A $\delta$  fibers.

\* The electric pulp tester delivers a current sufficient to overcome the resistance of enamel and dentin and stimulate the sensory A fibers at the dentin-pulp border zone. Smaller C fibers of the pulp do not respond to the conventional pulp tester because significantly more current is needed to stimulate them. Bender and associates found that in anterior teeth, the optimal placement site of the electrode is the incisal edge, as the response threshold is lowest at that location and increases as the electrode is moved toward the cervical region of the tooth.

A fibers have a relatively low threshold of excitability to external stimuli, and painful pulpitis is more likely to be associated with nociceptive C fiber activity indicative of pulpal tissue injury.

\*Of clinical interest is the evidence that nerve fibers of the pulp may be resistant to necrosis because their cell bodies are found in ganglia outside the pulp. Because nerve bundles in general are more resistant to autolysis than other tissue elements, even in degenerating pulps, C fibers might still be able to respond to noxious stimulation. It may be that C fibers remain excitable even after blood flow has been compromised in the diseased pulp, as C fibers are often able to function in the presence of hypoxia. This may explain why instrumentation of the

root canals of apparently nonvital teeth sometimes elicits pain. On the other hand, histologic studies on nonvital teeth failed to demonstrate high levels of innervation, leading to the suggestion that pain may be due to the transfer of noxious chemicals to terminals located in periapical tissues.

\*The sympathetic innervation of teeth derives from the superior cervical ganglion (SCG). Postganglionic sympathetic nerves travel with the internal carotid nerve, join the trigeminal nerve at the ganglion, and supply teeth and supporting structures via the maxillary and mandibular division of the trigeminal nerve. Sympathetic fibers appear with blood vessels at the time the vascular system is established in the dental papilla. In the adult tooth pulp, sympathetic fibers form plexuses, usually around pulpal arterioles. Stimulation of these fibers results in constriction of the arterioles and a decrease in blood flow. The sympathetic neuron terminals contain the classic neurotransmitter, norepinephrine (NE), and neuropeptide Y (NPY). Study showed that a reduction in pulpal blood flow, induced by stimulation of sympathetic fibers leading to the pulp, results in depressed excitability of pulpal A fibers. The excitability of C fibers is less affected than that of A fibers by a reduction in blood flow.

\*After generation of an action potential, not only is information sent to the CNS, but also in an antidromic fashion (i.e., in the reverse direction of the impulse) in which proinflammatory neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP), neurokinins, and the classic neurotransmitter, glutamate, are released from afferent terminals in the pulp and periradicular tissues.

\*Following the first step (detection of stimuli by nerve endings) afferent neurons synapse at trigeminal nuclear complex. In the trigeminal pain system, these action potentials arrive at the trigeminal spinal tract nuclear complex located in the medulla. Three distinct subnuclei can be found in this complex. Named for their anatomic position, they are the subnuclei oralis, interpolaris, and caudalis. Although the more rostral subnuclei (oralis and interpolaris) receive some nociceptive input from oral tissues, most such input is received at the level of the subnucleus caudalis. Because of its organizational similarity to the dorsal horn of the spinal cord (which receives nociceptive input from the somatosensory system), the subnucleus caudalis has been termed the medullary dorsal horn. Primary afferent fibers (whose cell bodies are located in the trigeminal ganglion) transmit signals to projection neurons in the medullary dorsal horn via the release of transmitters such as the excitatory amino acid, glutamate, and the neuropeptide, substance P. The cell bodies of the second-order (projection) neurons in the trigeminal pain system are found in the medullary dorsal horn; their processes cross the midline and project rostrally to the thalamus via the trigeminothalamic tract. From the thalamus, third-order neurons relay information to the cerebral cortex via a thalamocortical tract. Once signals have reached the cortex, the input may be perceived as pain. Evidence exists that referred pain is caused by convergence of afferent input from different areas onto the same projection neurons.

### **Neurogenic modulation (Pathways, ch.13):**

Of immense importance in pulp biology is the presence of neuropeptides in pulpal nerves. Pulpal nerve fibers contain neuropeptides such as calcitonin gene-related peptide (CGRP), substance P (SP), neuropeptide Y, neurokinin A (NKA), and VIP. SP and CGRP contribute to inflammation and promote wound healing. The release of CGRP can be modified by sympathetic agonists and antagonists, offering the promise of using such agonists to treat dental pain. This latter point is important because clinicians use sympathetic agonists every day—the vasoconstrictors present in local anesthetic solutions may have direct effects on inhibiting dental nerve activity. Local anesthetic reduction in pain may be due to the actions of both the local anesthetic and the vasoconstrictor. Neurogenic inflammation is mediated by the release of the neuropeptides calcitonin gene related peptide (CGRP) and substance P (SP) from nociceptors, which act directly on vascular endothelial and smooth muscle cells. CGRP produces vasodilation effects whereas SP increases capillary permeability leading to plasma extravasation and edema. On the other hand, neuropeptide (NPY) cause vasoconstriction.

### **Convergence theory (Pathways, ch.4, 17):**

Multiple primary afferent neurons may synapse on a single projection (i.e., convergence). This occurs to a much greater degree in deep tissues as opposed to cutaneous tissues. Primary afferent fibers of nontrigeminal origin such as those derived from vagus, glossopharyngeal, facial, and cervical spinal ganglia have been shown to converge and synapse onto trigeminal projection neurons located as far caudal as spinal level C4. This phenomenon of convergence may result in the clinical finding of pain that radiates beyond an area of tissue injury. Convergence may also explain why pain appears to be associated with a site other than the injured area (referred pain). Interestingly, when projection neurons receive input from superficial and deep structures, the more superficial inputs usually predominate. Thus, pain originating from deep structures would typically be referred to superficial areas (e.g., pain originating from the jaw muscles would typically be referred to the face rather than deeper structures). Evidence exists that referred pain is caused by convergence of afferent input from different areas onto the same projection neurons.

Approximately 50% of subnucleus caudalis neurons are estimated to receive convergence of sensory input from cutaneous and deep structures. In one study of a cat, a single nucleus caudalis neuron received input from sensory neurons innervating the cornea, the skin overlying the maxilla, a maxillary premolar tooth, and a mandibular canine and premolar tooth on one side. Subnuclei oralis and interpolaris also receive converging input from orofacial and muscle afferents. This would explain the clinical observation of patients who perceive pain in a particular tooth that actually originates from either a different tooth or structure. In such cases, anesthetizing the tooth suspected by the patient would afford no relief. However, if an

anesthetic is delivered selectively to the suspected primary source of pain, the patient's discomfort should greatly diminish. Likewise, if the source of a perceived toothache were located in a muscle of mastication, palpation of that muscle should aggravate the pain.

### **Sensitization (Pathways, ch.17):**

*Central sensitization* can be defined as an increased responsiveness of central nociceptive neurons to peripheral stimulation that occurs in addition to *peripheral sensitization* of the primary afferent nociceptors. Central sensitization is thought to be a major cause of hyperalgesia and allodynia.

In the peripheral sensitization, following repeated noxious stimuli, both A and polymodal C fiber nociceptors undergo a process of sensitization manifested by three obvious changes in response patterns. First, firing thresholds may decrease, so that previously non-noxious stimuli may trigger discharges, contributing to the sensation of pain (*allodynia*). Second, after-discharges may occur, so that noxious stimuli may produce an even greater increase in the perceived intensity of pain (*hyperalgesia*). And third, firing may occur spontaneously, contributing to the development of spontaneous pain. These changes are often seen in endodontic pain patients and may be explained in part by the effects of chemical mediators released into inflamed pulp and periradicular tissues. Such mediators include substances produced from damaged tissues, agents of vascular origin, and peptides released from the nerve fibers themselves.

The level and duration of pain prior to endodontic intervention have been cited in several studies as predictors of postoperative endodontic pain, and this may be due to such a prolonged and intense input from C nociceptors. Any reduction of such a barrage should limit the occurrence of central sensitization and the development of pain of longer duration after tissue injury (including surgical and nonsurgical endodontic procedures). The use of long-acting local anesthetics following tonsillectomies and third molar extractions has been shown to provide pain relief far beyond the duration of the peripheral tissue anesthesia

### **Hyperalgesia and Allodynia (Pathways, ch.17):**

Three characteristics of hyperalgesia are (1) spontaneous pain, (2) a decreased pain threshold, and (3) an increased response to a painful stimulus. The peripheral mechanisms for these symptoms include a decrease in firing threshold, an increase in responsiveness to noxious stimuli, and development of spontaneous discharges of nociceptors. All three of these characteristics can be seen in patients experiencing inflammatory pain of pulpal origin. It is recognized that hyperalgesia can be produced by sustained inflammation, as in the case of sunburned skin. Clinical observation has shown that the sensitivity of dentin often increases when the underlying pulp becomes acutely inflamed, and the tooth may be more difficult to anesthetize. This is due in part to the upregulation of tetrodotoxin-resistant (TTX-resistant) sodium channels in inflamed neural tissue. NGF seems to play an important role in hyperalgesia. NGF regulates chronic inflammatory hyperalgesia by controlling gene

expression in sensory neurons, including genes involved in inflammatory hyperalgesia in the dental pulp. Although a precise explanation for hyperalgesia is lacking, apparently localized elevations in tissue pressure and inflammatory mediators that accompany acute inflammation play an important role. Clinically, we know that when the pulp chamber of a painful tooth with an abscessed pulp is opened, drainage of exudate soon produces a reduction in the level of pain. This suggests that mechanical stimuli may contribute substantially to pain during inflammatory hyperalgesia.

Signs of Hyperalgesia	Related Diagnostic Tests or Symptoms
Spontaneous pain	Spontaneous pain
Reduced pain threshold	Percussion test, palpation test, throbbing pain
Increased response to painful stimuli	Increased response to pulp test (electric or thermal test)

From a clinical point of view, *thermal allodynia* is the term that best describes a patient whose chief complaint is “I have pain when I drink cold beverages.” *Mechanical allodynia* is involved when the chief complaint is “It now hurts when I bite on this tooth.” These previously non-noxious stimuli now cause the perception of pain. Hyperalgesia is manifested in endodontic pain patients when noxious stimuli (e.g., refrigerant sprays or carbon dioxide snow used in the cold test) produce much more pain than they would in teeth with normal pulp tissues. Spontaneous pain involves episodes of pain that seem to be unprovoked. All these changes can be partly explained by sensitization of peripheral nerve endings in the pulp and periradicular tissues.

### Referred pain (Pathways, ch.17):

Referred pain is pain felt in an area innervated by a nerve different from the one that mediates the primary pain. Referred pain cannot be provoked by stimulation of the area where the pain is felt; rather, it is brought on by manipulation of the primary source of pain. In addition, referred pain cannot be arrested unless the primary source of pain is anesthetized. The referral of pain tends to occur in a laminated fashion. This is because peripheral nociceptors enter the spinal trigeminal tract in a laminated fashion. As a result, there are general referral patterns in the face. In addition, the referral of pain is usually in a cephalad or upward direction. This is evidenced clinically in that pain from mandibular molars typically is referred to maxillary molars, as opposed to premolars or incisors.

Referred pain from a tooth is usually provoked by an intense stimulation of pulpal C fibers, the slow conducting nerves that when stimulated cause an intense, slow, dull pain. Anterior teeth seldom refer pain to other teeth or to opposite arches, whereas posterior teeth may refer pain to the opposite arch or to the periauricular area but seldom to the anterior teeth. Mandibular posterior teeth tend to transmit referred pain to the periauricular area more often than maxillary posterior teeth. One study showed that when second molars were stimulated with an electric

pulp tester, patients could discriminate accurately which arch the sensation was coming from only 85% of the time, compared with an accuracy level of 95% with first molars and 100% with anterior teeth. The investigators also pointed out that when patients first feel the sensation of pain, they are more likely to accurately discriminate the origin of the pain. With higher levels of discomfort, patients have less ability to accurately determine the source of the pain. Therefore, in cases of diffuse or referred pain, the history of where the patient first felt the pain may be significant.

### **Pulp blood flow regulation (Pathways, ch.12, 13):**

There are  $\alpha$ -adrenergic receptors in the pulp, and stimulation of the cervical sympathetic trunk causes vasoconstriction at the level of post-capillary arterioles and fall in pulpal blood flow that can be partially reversed by  $\alpha$ -receptor blockade. NPY, colocalized with norepinephrine in pulpal sympathetic nerve fibers, contributes also to vasoconstriction in the pulp.

Increase in pulpal blood flow is observed after electrical tooth stimulation and is caused by the release of sensory neuropeptides followed by vasodilatation. CGRP released from sensory nerve fibers is mainly responsible for the observed vasodilatation.

Glutamate, present in CGRP negative sensory afferent nerve fibers in the pulp, also has a vasodilatory effect when applied in the pulp during experimental conditions.

There is evidence for sympathetic modulation of sensory neuropeptide release in the dental pulp; presynaptic adrenoceptors are found on the sensory nerve terminals and attenuate the release of vasodilators from the sensory nerves.

Muscarinic receptors have been identified in the pulp, and the parasympathetic neurotransmitter acetylcholine (ACh) causes vasodilatation and increases blood flow in the tissue. The vasodilation evoked by acetylcholine has been demonstrated to be partly dependent on nitric oxide (NO) production.

VIP, which coexists with ACh in postganglionic neurons, is found in the dental pulp and has been demonstrated to cause vasodilatation and increase in pulpal blood flow in cats.

On the other hand, Sasano and coworkers failed to demonstrate parasympathetic nerve-evoked vasodilatation in the cat dental pulp, leaving pulpal vascular responses to parasympathetic neurotransmitters with some uncertainty.

### Local control of blood flow:

The microvascular bed in the dental pulp has the ability to regulate hemodynamics in response to local tissue demands. Endothelin-1 is located in the endothelium of pulpal vasculature, and close intraarterial infusions of endothelin-1 reduce pulpal blood flow. However, endothelin-1 does not seem to influence blood vessel vascular tone under basal, resting conditions.

The endothelium in pulpal blood vessels modulates vascular tone by release of vasodilators such as prostacyclin and NO. A basal synthesis of NO provides a vasodilator tone on pulpal vessels. The shear forces that blood flow exert on endothelial cells seem to regulate the release of NO.

Adenosine is released from ischemic and hypoxic tissue and is probably important in the metabolic regulation of blood flow in periods of low pulpal oxygen tension. When applied from the extraluminal side of the vessel wall, adenosine mediates vasodilatation in pulpal vessels.

Inflammation in the pulp takes place in a low-compliance environment composed of rigid dentinal walls. *Compliance* is defined as the relationship between volume (V) and interstitial pressure (P) changes:  $C = \Delta V / \Delta P$ . Consequently, in the low-compliant pulp, an increase in blood or interstitial volume will lead to a relatively large increase in the hydrostatic pressure in the pulp. The acute vascular reactions to an inflammatory stimulus are vasodilatation and increased vascular permeability, both of which will increase pulp interstitial fluid pressure and may tend to compress blood vessels and counteract a beneficial blood flow increase.

Classical studies have demonstrated that an increase in intrapulpal tissue pressure promoted absorption of tissue fluid back into the circulation, thereby reducing the pressure. This observation can explain why pulpal tissue pressure in inflamed pulps may persist in local regions for long observation periods, contradicting the old concept of a wide, generalized collapse of pulpal venules and cessation of blood flow (pulpal strangulation theory).

The delivery of dental restorative procedures may lead to substantial increases or decreases in pulpal blood flow, depending on the precise procedure and time point sampled. Vasoactive mediators are locally released upon an inflammatory insult, and in the pulp, prostaglandin E<sub>2</sub>, bradykinin, SP, and histamine have all been demonstrated to increase pulpal blood flow after application. In contrast, serotonin (5-HT) is released primarily from the platelets, and given intraarterially, it has been shown to reduce pulpal blood flow. Also, expression of TNF- $\alpha$ , IL-1 $\beta$ , and IFN- $\gamma$  following inflammation can significantly increase vascular permeability.

### **Pulp immunity (Pathways, ch.12, 13, 15):**

Three basic reactions tend to protect the pulp against caries: (1) a decrease in dentin permeability, (2) tertiary dentin formation, and (3) inflammatory and immune reactions

The early inflammatory response to caries is characterized by the focal accumulation of chronic inflammatory cells. This is mediated initially by odontoblasts and later by dendritic cells. Recent studies have demonstrated that pulp dendritic cell can migrate to regional lymph nodes, for antigen presentation. In vitro studies have suggested that the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) and osteopontin by dendritic cells and macrophages represents a mechanism whereby they contribute to odontoblast differentiation. Evidence suggests that odontoblasts also play a role in the humoral immune response to caries.

### **Specificity of Innate Immune Response:**

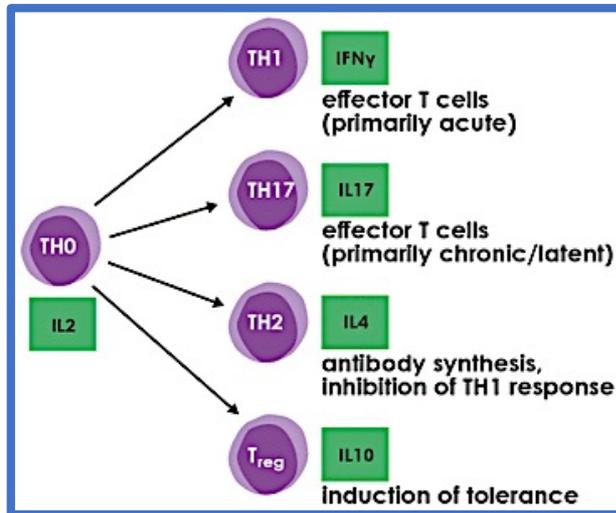
In recent years, the concept of the nonspecific nature of innate immunity has changed since identification of a network of germline-encoded receptors, the pattern-recognition receptors (PRRs), that recognize specific molecular motifs of microorganisms. PRRs can be expressed on the cell surface (macrophages, dendritic cells, neutrophils, NK cells, B cells), in intracellular compartments, or secreted into the blood and tissue fluids. There are numerous microbial constitutive and conserved products such as the pathogen-associated molecular patterns (PAMPs), also noted earlier. Importantly, the PRRs of the innate immune system recognize PAMPs.

The specificity of innate immunity is due to the recognition of PAMPs of microorganisms by PRRs, such as Toll-like receptors (TLRs), of the host's cells. Activation of PRRs triggers numerous host responses, including opsonization, activation of complement and coagulation cascades, phagocytosis, activation of proinflammatory signaling pathways, and induction of apoptosis.

Bacterial toxins (e.g., lipopolysaccharide [LPS], lipoteichoic acid [LTA]) and noxious metabolic by-products that egress from the root canal system into the periapical tissues are capable of inducing a periapical inflammatory reaction. These substances can activate the innate immune system via receptors that recognize the stereotypic pathogen-associated molecular patterns (PAMPs) that are found in the structure of these toxins. Different classes of microbes express different molecular patterns that are recognized by different pattern recognition receptors (PRRs) or Toll-like receptors (TLRs) on host cells, such as phagocytes, dendritic cells, and B lymphocytes. PRRs or TLRs are encoded in the germline. In mammalian species, there are at least 10 TLRs, and each appears to have a distinct function in innate immune recognition. For example, LPS can stimulate sensory nerve fibers to release calcitonin gene-related peptide (CGRP) and substance P (SP) to cause vasodilation and increased vascular permeability. LPS and lipoproteins can also activate TLRs on dendritic cells to

stimulate T lymphocyte differentiation. Certain subtypes of TLRs recognize the common shared structural features of various toxins (i.e., PAMPS). Because the TLRs are synthesized before an infection, they are classified as part of the innate immune system.

### Adaptive/Specific Immune Response



T-cell antigen receptor (TCR) on T cells interact with antigens that are presented by antigen presenting cells (such as macrophages, dendritic cells) expressing MHC molecules along with other accessory molecules, whereas BCRs on B cells interact with antigens directly. B-cell antigen receptor (BCRs) may be secreted in the blood circulation or in the tissues as antibodies.

The interaction between TCR and the antigen peptide/MHC complex and co-stimulators activates T cells, leading to the synthesis of T-cell growth factor, IL-2, and its receptor that causes T-cell clonal expansion/proliferation. There are a number of T-cell subpopulations, categorized by their functions: (1) T helper cells (TH), (2) T regulatory cells (Treg), (3) T suppressor cells (TS), and (4) T cytotoxic (cytolytic) (TC) cells.

Upon antigen stimulation, naive CD4 T cells proliferate and differentiate into TH1 or TH2 cells. Each subset of TH cells has distinct functions and cytokine profiles. TH1 cells mainly produce IL-2 and interferon (IFN)- $\gamma$ , which activate macrophages and induce B cells to produce opsonizing antibody. TH2 cells produce IL-4, -5, -10, and -13, which activate B cells to make neutralizing antibody. TH17 also develop under the activation of IL-6 and TGF- $\beta$  and produce IL-17, a powerful pro-inflammatory cytokine. Overall, TH1 and TH2 have mutually inhibitory effects. The development of CD4 TH cells involves the encounter of antigen presented by antigen-presenting cells (APCs) in association with class II MHC. All cells express MHC class I, but only certain cells express class II MHC. These class II MHC-expressing cells constitute the body's population of APCs and consist of (1) dendritic cells, (2) macrophages, (3) B cells, (4) vascular endothelial cells, and (5) epithelial cells.

T cytotoxic cells (CD8+TC), also known as cytolytic T lymphocytes (CTLs), are a subset of T cells that kill target cells expressing MHC-associated peptide antigens. The majority of TC express CD8 and recognize antigens degraded in the cytosol and expressed on the cell surface in association with class I MHC molecules of the target cells.

The role of B cells in adaptive immunity is mainly the production of antibodies that constitute the host humoral immune response. A large quantity of antibody is secreted when B cells terminally differentiate into plasma cells. The ability of antigens to selectively stimulate the differentiation of plasma cells supports the clinical finding that plasma cells isolated from periapical lesions secrete antibodies specific for the particular bacteria found in the adjacent root canal system. Therefore, both T and B cells mediate the observed immune responses in pulpal and apical pathosis.

**NF- $\kappa$ B** (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival and is the main transcriptional factor involved in the inflammatory responses. Upon recognition of LPS by Toll-like receptors (TLRs) 4 and LTA by TLRs 2, NF- $\kappa$ B will be activated and increase the expression of inflammatory cytokines.

**The complement system** consists of some 20 interactive plasma and cell membrane proteins. Once activated, complement is a potent effector mechanism for:

1. Mediating vascular responses (histamine release) (Transportation/ supplies)
2. Recruiting phagocytic leukocytes (chemotaxis)
3. Opsonizing targets of phagocytic cells
4. Directly damaging target cells.

The system is activated in a sequence that sort of cascades along, once started up. Therefore, it comprises a number of steps of component pieces. The activation of C3 is the most critical step. C3 can be activated by either the classic pathway or the alternative pathway.

The classic pathway:

This pathway is activated by antibody-coated targets or antigen- antibody complexes. The antibodies involved are IgM or IgG. The chief function of C1, C4, and C2 is to form a C3-cleaving enzyme. IgM or IgG binds to and activates C1 (C1 is composed of subunits C1q, C1r, and C1s). C1 q bound to antibody has enzymatic activity and is termed C1 esterase. Its role is to cleave C4 and C2. C1 esterase inhibitor is a regulatory plasma protein that binds to activated C1 and destroys its enzymatic activity. Patients with hereditary deficiency of this inhibitor develop hereditary angioedema when subjected to trauma or stress. This results in generalized edema. Patients with this condition sometimes die of asphyxiation. When an antigen-antibody complex binds to C1 q, C4 and C2 are cleaved. This results in formation of a complex C4b2a, which is termed C3 convertase. C3 convertase has the ability to cleave C3 into two biologically important fragments, C3a and C3b. The activation of C3 results in another cleavage. The

products are called C3a and C3b. C3a is called anaphylatoxin, and it causes the release of histamine from mast cells and basophils. This results in vasodilation and increased vascular permeability. C3b serves to continue the cascade of events of complement. Its release results in the activation of the terminal components, C5 to C9. Cleavage of C5 yields C5a and C5b. C5a is another anaphylatoxin that mediates the same vascular responses caused by C3a. The terminal complement sequence C5 to C9 produces a series of reactions. Fixation of C8 and C9 to antibody-coated cells such as bacteria and some mammalian cells (eg, erythrocytes, tumor cells, etc) causes lysis of the cells. C5b interacts with, and is stabilized by, C6 to initiate the membrane attack complex (MAC) composed of C5b-C9. The assembly of C5b-C8 appears to form a small channel in the target cell membrane that is increasingly enlarged and stabilized by the binding of multiple molecules of C9. One MAC penetrating the erythrocyte cell membrane is sufficient to destroy the cell.

Both pathways involve the splitting of C3 to C3a and C3b. This requires an enzyme, C3 convertase. Thus, the activation of either the classic pathway or the alternative pathway results in the formation of a C3 convertase.

In acute inflammatory reactions in which complement is involved, cleavage of C3 is the most important event.

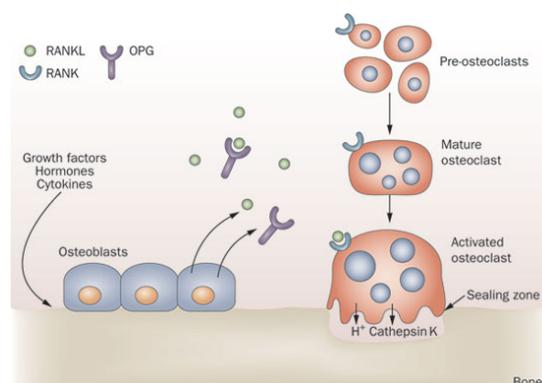
## Bone Hemostasis:

Bone homeostasis is regulated by many factors, including prostaglandins (PGs). PGs are important to both normal and pathologic bone turnover. PGs modulate osteoblast proliferation and differentiated functions. The levels of prostaglandins E (PGE) and F (PGF) are elevated in the early phase of fracture healing, and administration of PGE<sub>2</sub> has increased the rate of osseous repair in several animal studies. NSAID inhibition of the enzyme cyclooxygenase (COX), which is involved in the synthesis of PGs, is the same mechanism by which NSAIDs control pain. By inhibiting the COX enzymes and the subsequent production of prostaglandins, NSAIDs accomplish the desired anti-inflammatory effects—but also prevent the increased production of PGs required for bone healing. In vitro studies using animal models have shown that NSAIDs inhibit osteoblast proliferation and stimulate protein synthesis.

### **RANK/RANKL and OPG role in bone remodeling (Pathways, ch.15):**

Bone resorption is caused by osteoclasts. **Osteoclasts** are large multinucleated cells, with a 'ruffled border' that resorb bone matrix, as shown in the diagram above. They are important for remodelling, growth and repair of bone. (clast - greek 'to break'). The formation of osteoclasts involves differentiation of the osteoclast precursor from the monocyte-macrophage cell lineage in bone marrow. Several cytokines and growth factors, such as granulocyte/macrophage colony-stimulating factor (GM-CSF), RANKL (receptor activator of nuclear factor  $\kappa$ B ligand), IL-1, IL-6, TNF, as well as prostaglandins, bradykinin, kallidin, and thrombin, have been shown to mediate osteoclast progenitor cell differentiation. In vitro studies have suggested that the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) and osteopontin by dendritic cells and macrophages represents a mechanism whereby they contribute to odontoblast differentiation to osteoclast. RANKL are expressed by osteoblasts and T-cells. Therefore, osteoblasts are required for osteoclast activation.

Osteoprotegerin (OPG) protects the skeleton from excessive bone resorption by binding to RANKL and preventing it from binding to its receptor, RANK. Thus, RANKL/OPG ratio is an important determinant of bone mass and skeletal integrity. OPG can reduce the production of osteoclasts by inhibiting the differentiation of osteoclast precursors. Denosumab is an osteoporosis treatment designed to target RANKL. It is a fully human monoclonal antibody (IgG2) that binds to RANKL with high affinity and specificity. It blocks the interaction of RANKL with RANK, mimicking osteoprotegerin.



### **Osteoclast histology in active resorptive area:**

Osteoclasts are motile, multinucleated giant cells that are responsible for bone resorption. They are formed by the fusion of mononuclear precursor cells of the monocyte-macrophage lineage derived from the spleen or bone marrow; osteoblasts and osteocytes, on the other hand, are derived from skeletal precursor cells. Osteoclasts are recruited to the site of injury or irritation by the release of many pro-inflammatory cytokines. To perform their function, osteoclasts must attach themselves to the bone surface. On contact with mineralized extracellular matrices, the actin cytoskeleton of an actively resorbing osteoclast is reorganized to produce an organelle-free zone of sealing cytoplasm (clear zone) associated with the osteoclast's cell membrane; this enables the osteoclast to achieve intimate contact with the hard tissue surface.<sup>92</sup> The clear zone surrounds a series of fingerlike projections (podosomes) of cell membrane, known as the ruffled border, beneath which bone resorption occurs. The resorptive area within the clear zone, therefore, is isolated from the extracellular environment, creating an acidic microenvironment for the resorption of hard tissues.

### **Bone morphogenic protein in Endodontics** (M Nakashima, 2005):

Bone morphogenetic proteins (BMPs) are multi-functional growth factors that belong to the transforming growth factor beta (TGFbeta) superfamily. The key elements of dentin regeneration are stem cells, morphogens such as bone morphogenetic proteins (BMPs) and a scaffold of extracellular matrix. The dental pulp has stem/progenitor cells that have the potential to differentiate into dentin-forming odontoblasts in response to BMPs. Pulpal wound healing consists of stem/progenitor cells release from dental pulp niche after noxious stimuli such as caries, migration to the injured site, proliferation and differentiation into odontoblasts. There are two main strategies for pulp therapy to regenerate dentin: (1) in vivo method of enhancing the natural healing potential of pulp tissue by application of BMP proteins or BMP genes, (2) ex vivo method of isolation of stem/progenitor cells, differentiation with BMP proteins or BMP genes and transplantation to the tooth.

**Osteocalcin**, also known as is a non-collagenous protein found in bone and dentin. Osteocalcin is secreted solely by osteoblasts and thought to play a role in the body's metabolic regulation and is pro-osteoblastic, or bone-building. During the dentin formation or regeneration process the expression of osteocalcin by odontoblasts are increased. Osteocalcin is a biomarker for bone and dentin regeneration.

## Non-odontogenic pain; Source and explanation

### **(Pathways, ch.15)**

The possible source of non-odontogenic pains can be classified in the following groups:

- Musculoskeletal and other non-progressive pains arising from somatic structures
- Neurovascular pain, otherwise known as headache disorders
- Neuropathic pain
- Pain of purely psychologic origin, otherwise known as psychogenic toothache
- Pain associated with a pathologic process

Non-odontogenic pains can be suspected using following clues:

- Difficult for patients to respond to history taking because their words do not adequately describe what they feel; therefore, time may be needed to obtain the necessary information
- Poorly localized to a region within the dentoalveolar structures
- Pain is perceived to be deep in the tissues, rather than on the surface
- Continuous pain, one that never stops and seems to always be there
- Pain has the sensation of feeling pressure with a dull ache quality
- Complex and confounding descriptors, such as itching, tingling, or pricking, are sometimes present
- Doesn't not follow normal nerve distribution

### **Cluster headaches:**

is rare neurovascular disorders that are strictly unilateral pains defined by the concurrent presentation of at least one ipsilateral autonomic symptom—such as nasal congestion, rhinorrhea, lacrimation, eyelid edema, periorbital swelling, facial erythema, ptosis, or miosis—that occurs with the pain. The major distinguishing features between these headache disorders are the duration and frequency of the pain episodes, as well as the gender most often afflicted. Cluster headache is the most common of the group, occurring in men three to four times more often than in women, with pain episodes lasting between 15 minutes and 2 hours that occur at a frequency of eight episodes per day to one every other day. These headaches come in clusters, with active periods of 2 weeks to 3 months, thus the name. Elimination of pain after 10 minutes with inhalation of 100% oxygen is diagnostic for cluster headache,

whereas sublingual ergotamine and sumatriptan are also effective acute treatments for cluster headache. Paroxysmal hemicrania, which has a 3:1 female predilection, presents with characteristics similar to those of cluster headache but with a frequency of more than five per day and a duration lasting 2 to 30 minutes. This headache disorder has a 100% response to indomethacin but is refractory to other treatments, thus underscoring the need for obtaining an accurate diagnosis from an experienced clinician.

### **Temporal arthritis:**

Vascular structures within the craniofacial region have also been reported to present as nonodontogenic toothache, with arteritis being the pain-provoking pathology. These pains have been described as a continuous dull pain that can sometimes be made worse with jaw function. The stereotypical presentation includes a history of eyesight changes, such as blurred vision, and the examination feature of pulseless, indurated temporal arteries that are painful to palpation. A laboratory finding of an elevated erythrocyte sedimentation rate (ESR) is suggestive of the disorder, and diagnosis is confirmed by temporal artery biopsy. Treatment includes administration of corticosteroids; therefore, because permanent blindness is a possible sequela if cranial arteries are left unmanaged, immediate referral to the appropriate medical colleague is indicated.

### **Trigeminal neuralgia:**

is characteristically an intense, sharp shooting pain that is most often unilateral. Ipsilateral to the perceived location of the symptoms is an area that, on stimulation such as light touch, elicits sharp shooting pain. The area that elicits the pain is referred to as a trigger zone, and it can be in the distribution of the resultant pain or in a different distribution—but is always ipsilateral. Although most patients present with a characteristic trigger zone, not all patients will present with this finding. An important characteristic of trigger zones is that the response to the stimulus is not proportional to the intensity of the stimulus—that is, slight pressure on a trigger zone results in severe pain. In addition, once triggered, pain typically subsides within a few minutes until triggered again. This is in contrast to odontogenic pain, which may come and go but does not do so in such a predictable and repeatable manner. Finally, the trigger for odontogenic pain is an area that has no sensory abnormalities (e.g., dysesthesia or paresthesia).

## Microbial Identification

**(Pathways, ch.14)** The endodontic microbiota has been traditionally investigated by microbiologic culture methods. Endodontic samples are collected and transported to the laboratory in a viability-preserving, nonsupportive, anaerobic medium. After a suitable period of incubation, individual colonies are subcultivated and identified on the basis of multiple phenotype-based aspects, including colony and cellular morphology, gram-staining pattern, oxygen tolerance. Following table depicts advantage and disadvantages for culturing technique:

Advantages	Limitations
Broad-range nature, identification of unexpected species	Impossibility of culturing a large number of extant bacterial species
Allow quantification of all major viable cultivable microorganisms in samples	Not all viable bacteria can be recovered
Allow determination of antimicrobial susceptibilities of isolates	Once isolated, bacteria require identification using a number of techniques
Physiologic studies are possible	Misidentification of strains with ambiguous or aberrant phenotypic behavior
Pathogenicity studies are possible	Low sensitivity
Widely available	Strict dependence on the mode of sample transport
	Samples require immediate processing
	Costly, time consuming, and laborious, as for cultivation of anaerobes
	Specificity is dependent on experience of microbiologist
	Extensive expertise and specialized equipment needed to isolate anaerobes
	Takes several days to weeks to identify most anaerobes

Molecular technology has also been applied to reliably identify cultivated bacteria, including strains with ambiguous or aberrant phenotypic behavior, rare isolates, poorly described or uncharacterized bacteria, and newly named species. Molecular approaches for microbial identification rely on certain genes that contain revealing information about the microbial identity. Of the several genes that have been chosen as targets for bacterial identification, the 16S rRNA gene (or 16S rDNA) has been the most widely used. Data from 16S rRNA gene sequences can be used for accurate and rapid identification of known and unknown bacterial species, using techniques that do not require cultivation. The 16S RNA gene of virtually all

bacterial species in a given environment, including still uncultivated and uncharacterized bacteria, can be amplified by polymerase chain reaction (PCR) using broad-range (or universal) primers that are complementary to conserved regions of this gene. Following table shows the pros and cons of molecular techniques.

Advantages	Limitations
<p>Detect both cultivable and as-yet-uncultivated species or strains</p> <p>High specificity and accurate identification of strains with ambiguous or aberrant phenotypic behavior</p> <p>Detect species directly in clinical samples</p> <p>High sensitivity</p> <p>Rapid; most assays take no more than minutes to a few hours to identify a microbial species</p> <p>Do not require carefully controlled anaerobic conditions during sampling and transportation</p> <p>Can be used during antimicrobial treatment</p> <p>Anaerobic handling and expertise not required</p> <p>Samples can be stored frozen for later analysis</p> <p>DNA can be transported easily between laboratories</p> <p>Detect dead microorganisms</p>	<p>Most assays are qualitative or semiquantitative (exceptions: real-time PCR)</p> <p>Most assays only detect one species or a few different species at a time (exceptions: broad-range PCR, checkerboard, microarray)</p> <p>Most assays detect only the target species and fail to detect unexpected species (exception: broad-range PCR)</p> <p>Some assays can be laborious and costly (e.g., broad-range PCR)</p> <p>Biases in broad-range PCR introduced by homogenization procedures, preferential DNA amplification, and differential DNA extraction</p> <p>Hybridization assays using whole genome probes detect only cultivable species</p> <p>Can be very expensive</p>

## Management of medically compromised patients

### 1) Hypertension and their management by oral health care providers:

Classification of Blood Pressure in Adults and Recommendations for Follow-up			
BP Classification	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Recommended Follow-up
Normal	<120	and <80	Recheck in 2 years
Prehypertension	120-139	or 80-89	Recheck in 1 year
Stage 1 hypertension	140-159	or 90-99	Confirm within 2 months
Stage 2 hypertension	≥160	or ≥100	Evaluate or refer to source of care within 1 month. For those with higher pressures (e.g., >180/110 mm Hg), evaluate and treat immediately or within 1 week, depending on the clinical situation and complications

For patients with BP <180/110, and no evidence of target organ involvement, any treatment may be provided, for patients with BP 180/110, defer elective dental care. For patients with target organ involvement, refer to appropriate chapter for management recommendations. For patients who are taking a nonselective beta blocker, limit epinephrine to 2 cartridges of 1:100,000 epinephrine (0.036). Also, it should be mentioned that presence of calcified atheroma detected on panoramic radiographs of individuals might be indicator of future risk of strokes.

list of drugs used for management of Hypertension:

Drugs (class)	Interaction with	Mechanism	Effect
β-Blockers	verapamil diltiazem	Additive effects	A-V conduction impaired; risk of A-V block
	oral antidiabetics	β <sub>2</sub> -receptor blockade	symptoms of hypoglycaemia are suppressed
	broncho-spasmolytic agents	β <sub>2</sub> -receptor blockade	suppression of the bronchospasmolytic effect
	dobutamine	β <sub>1</sub> -receptor antagonism	the inotropic action of dobutamine is inhibited
Thiazid diuretics	digoxin	Hypokalaemia	digoxin becomes more toxic (arrhythmogenic)
	lithium ions	renal excretion of lithium ions impaired	accumulation of lithium ions
α-Blockers	noradrenaline	α <sub>1</sub> -receptor blockade	noradrenaline shows less vasoconstrictor activity
Calcium antagonists			
Verapamil, diltiazem	β-Blocker	additive effect	A-V conduction impaired; risk of A-V block
	digoxin	renal excretion of digoxin	digoxin may accumulate; arrhythmogenic effect
	protease inhibitors (HIV-treatment)	inhibition of hepatic degradation	accumulation of verapamil or diltiazem
	cimetidine	ibid.	ibid.
DihydropyridineCa-antagonists	β-blocker	β-receptor blockade	suppression of reflex tachycardia (favourable)
Felodipine	Grapefruit Juice	Enzymic inhibition (Cyt.L450 system)	accumulation of felodipine
ACE-inhibitors	diuretics (thiazide)	additive effect	strong hypotensive action
	Diuretics (K <sup>+</sup> -sparing)	reduced renal excretion of K <sup>+</sup>	hyperkalemia
	NSAID's including high dose ASA	retention of Na <sup>+</sup> and H <sub>2</sub> O	reduced antihypertensive effects
	lithium ions	Reduced excretion of lithium ions	lithium ions accumulate
AT <sub>1</sub> -receptor antagonists	virtually the same as ACE-inhibitors	interactions as ACEi-s (see above)	described before
Centrally acting antihypertensives			
α-methyl-DOPA	Fe <sup>2+</sup> -ions	enteral absorption of α-methyl-DOPA	reduced antihypertensive action
clonidine	tricyclic antidepressants	antagonism of central α <sub>2</sub> -adrenoceptors	ibid.
	β-blockers	unknown	the clonidine rebound phenomenon is more frequent
both clonidine and α-methyl-DOPA	centrally acting depressant agents (hypnotics, tranquilizers, neuroleptics, anti-epileptics, some anti-depressants, H1-anti-histaminic agents, alcohol)	additive effect, non-specific	sedation, fatigue

**\*Recent Myocardial Infarction (<1 month) (major risk)**

Elective dental care should be deferred; if care becomes necessary, it should be provided in consultation with the physician. Management may include establishment of an IV line; sedation; monitoring of electrocardiogram, pulse oximeter, and blood pressure; oxygen; cautious use of vasoconstrictors; and prophylactic nitroglycerin.

**Past Myocardial Infarction (>1 month without symptoms) (intermediate risk)**

Elective dental care may be provided with the following management considerations: For stress/anxiety reduction: Provide oral sedative premedication and/or inhalation sedation if indicated, assess pretreatment vital signs and availability of nitroglycerin, and limit the quantity of vasoconstrictor used. For patients who are taking a nonselective beta blocker: Limit epinephrine to 2 cartridges of 1:100,000 epinephrine.

Antibiotic prophylaxis is not recommended for patients with a history of coronary artery bypass graft (CABG), angioplasty, stent or history of MI.

- Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis for Which Prophylaxis With Dental Procedures Is Recommended
- Prosthetic cardiac valve
  - Previous infective endocarditis
  - Congenital heart disease (CHD)<sup>†</sup>
    - Unrepaired cyanotic CHD, including those with palliative shunts and conduits
    - Completely repaired CHD with prosthetic material or device by surgery or catheter intervention during the first 6 months after the procedure\*
    - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device, which inhibits endothelialization
  - Cardiac transplantation recipients who develop cardiac valvulopathy

**\*Isosorbide mononitrate** is a drug of choice for treating angina. It works by dilating the blood vessels so as to reduce the blood pressure. This drug interacts with Sildenafil (Viagra) that can lead to life threatening hypotension. Verapamil belongs to a class of drugs called calcium channel blockers and is also a drug of choice for treating angina. This group of drugs lead to muscle relaxation and reduce the heart working load. This group is used to treat hypertension, angina. Along with other calcium channel blockers, verapamil is known to induce gingival hyperplasia.

## Types of Adrenergic Receptors:

### Alpha

contraction of smooth muscle in blood vessels  
vasoconstriction

Alpha 1 → excitatory; post-synaptic

Alpha 2 → inhibitory; post-synaptic

### Beta

smooth muscle relaxation  
vasodilation/bronchodilation  
cardiac stimulation, i.e., increased  
rate and strength of contraction

Beta 1. found in heart and small intestines. produces cardiac stimulation and lipolysis

Beta 2. found in bronchi of the lung, vascular beds and uterus produces bronchodilation and vasodilation

Epinephrine: Acts directly on Alpha and Beta receptors/ Beta effects predominate/ Increases force and rate of contraction / Increases stroke volume/ Increases myocardial O<sub>2</sub> use / Increases cardiac output / heart rate / Increases dysrhythmias and PVCs / Increases coronary artery perfusion / Increases systolic blood pressure / Decrease in cardiac efficiency

1.8 ml Cartridge of 2% Lidocaine 1:100,000 epi contains 0.018mg epi

Maximum Epinephrine: 11 Cartridges

Maximum Anesthetic: 300 mg

1.8 ml Cartridge of 2% Lidocaine 1:200,000 epi

Maximum Epinephrine: 22 Cartridges

Maximum Anesthetic: 300 mg

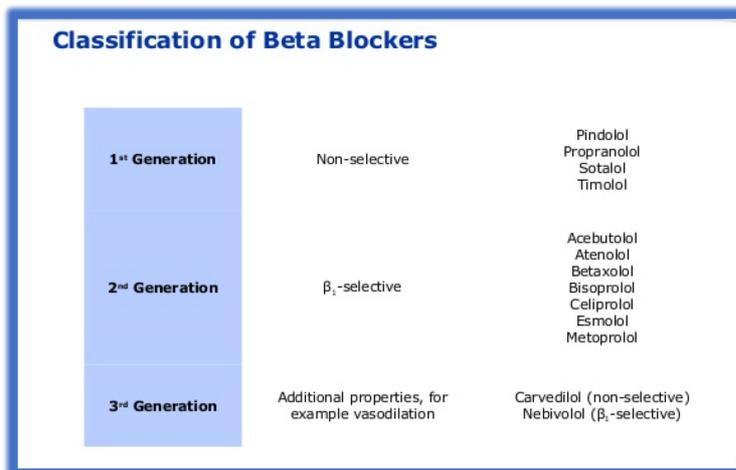
The maximum amount of 2% Lidocaine 1:100,000 epinephrine that can be used is 300 mg which is 8.3 cartridges regardless of the patient's weight; so, the maximum epinephrine will only be achieved after you have already surpassed the maximum amount of anesthetic allowable.

Levonordefrin is a synthetic vasoconstrictor. Acts through direct Alpha receptor stimulation (75%). Acts through some Beta activity (25%). Levonordefrin produces less cardiac and CNS stimulation than epinephrine. Levonordefrin is only 1/6 as strong as Epinephrine.

\*Metabolism of certain local anesthetics (e.g., prilocaine, benzocaine, articaine, and to a lesser extent lidocaine) can produce a metabolite that causes methemoglobinemia; this effect often occurs several hours after injection of the local anesthetic. Typical signs and symptoms include cyanosis, dyspnea, emesis, and headache. In a study on benzocaine-induced methemoglobinemia, 67% of reported adverse effects of benzocaine were associated with methemoglobinemia; of these events, 93% occurred with spray formulations of benzocaine, and only one case involved the gel formulation. Methylene blue is the primary emergency treatment for documented symptomatic methemoglobinemia. It is given in a dose of 1-2 mg/kg (up to a total of 50 mg in adults, adolescents, and older children) as a 1% solution in IV saline over 3-5 minutes.

### Beta blockers:

The first generation of beta-blockers were non-selective, meaning that they blocked both beta1 (b1) and beta2 (b2) adrenoceptors. Second generation beta-blockers are more cardio selective in that they are relatively selective for b1 adrenoceptors. Note that this relative selectivity can be lost at higher drug doses. Finally, the third-generation beta-blockers are drugs that also possess vasodilator actions through blockade of vascular alpha-adrenoceptors.



Propranolol is a non-selective beta blocker that can affect both receptors on large vessels and heart. By injecting EPI, epi can activate both Beta and Alpha receptors. However due to inhibitory effect of propranolol on beta receptors, Epi will lead to alpha activation and increase in BP. This will lead to compensatory drop in heart rate.

## 2)Heart failure:

HF is caused by the inability of the heart to function efficiently as a pump, which results in inadequate emptying of the ventricles during systole or incomplete filling of the ventricles during diastole. HF may result from acute injury to the heart, such as from myocardial infarction, or more commonly, from a chronic process, such as hypertension or cardiomyopathy.

The outstanding symptom of left ventricular failure is dyspnea, which results from accumulation or congestion of blood within the pulmonary vessels thus, the term congestive heart failure. Acute pulmonary edema is often the result of left ventricular failure (Because the blood returns from pulmonary veins to the left side of heart). Left-sided heart failure leads to pulmonary hypertension, which increases the work of the right ventricle as it pumps against increased pressure and often leads to right-sided heart failure. The most common cause of right-sided heart failure is preceding failure of the left ventricle. Outcomes of right ventricular failure consist of systemic venous congestion and peripheral edema

### NYHA Classification of Heart Failure

- **Class I:** No limitation of physical activity. No dyspnea, fatigue, or palpitations with ordinary physical activity.
- **Class II:** Slight limitation of physical activity. These patients have fatigue, palpitations, and dyspnea with ordinary physical activity but are comfortable at rest.
- **Class III:** Marked limitation of activity. Less than ordinary physical activity results in symptoms, but patients are comfortable at rest.
- **Class IV:** Symptoms are present at rest, and any physical exertion exacerbates the symptoms.

Medical treatment includes any treatment that can reduce the work load of the heart. diuretics, ACEI ( Captopril, isinopril, etc.), beta blockers and digoxin. Erythromycin and clarithromycin may increase the toxic effects of digoxin and should be avoid.

### Dental Management of the Patient With Heart Failure

- Evaluate patient for history, signs, or symptoms of heart failure (HF).
- For patients with symptoms of untreated or uncontrolled HF, defer elective dental care and refer to physician.
- For patients diagnosed and treated for HF:
  - Confirm status with patient or physician
  - New York Heart Association (NYHA) class I patients (asymptomatic)—Provide routine care.
  - NYHA class II (and some class III patients)—Obtain consultation with physician for medical clearance and provide routine care.
  - NYHA (some class III and class IV) patients—Obtain consultation with physician; consider treatment in a special care or hospital setting.
  - Identify underlying cardiovascular disease (i.e., coronary artery disease, hypertension, cardiomyopathy, valvular disease), and manage appropriately.
- Drug considerations:
  - For patients taking digitalis, avoid epinephrine; if considered essential, use cautiously (maximum 0.036 mg epinephrine or 0.20 mg levonordefrin); avoid gag reflex; avoid erythromycin and clarithromycin, which may increase the absorption of digitalis and lead to toxicity.
  - For patients with NYHA class III and IV congestive heart failure, avoid use of vasoconstrictors; if use is considered essential, discuss with physician.
  - Avoid epinephrine-impregnated retraction cord.
- See Table 6-1 for drug considerations and adverse effects.
- Schedule short, stress-free appointments.
- Use semisupine or upright chair position.
- Watch for orthostatic hypotension, make position or chair changes slowly, and assist patient into and out of chair.
- Avoid the use of nonsteroidal antiinflammatory drugs (NSAIDs).
- Watch for signs of digitalis toxicity (i.e., tachycardia, hypersalivation, visual disturbances, etc.).
- Nitrous oxide/oxygen sedation may be used with a minimum of 30% oxygen.

### 3)End-stage renal disease (ESRD):

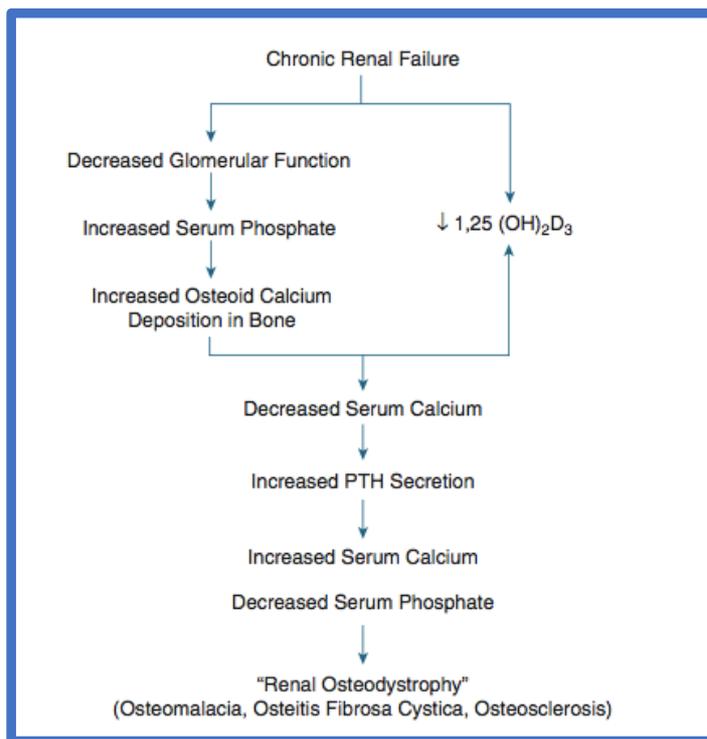
ESRD refers to bilateral, progressive, chronic deterioration of nephrons, the functional unit of the kidney. ESRD is caused by any condition that destroys nephrons. The three most common known causes of ESRD are diabetes mellitus (34%), hypertension (25%), and chronic glomerulonephritis (16%).

Consultation with the patient's physician is suggested before dental care is provided to patients under care for ESRD. Problems generally do not occur in provision of outpatient dental care if the patient's disease is well controlled and conservative medical care is provided. However, if the patient is in the advanced stages of failure or has another systemic disease common to renal failure (e.g., diabetes mellitus, hypertension, systemic lupus erythematosus), or if electrolyte imbalance is present, dental care may best be provided after physician consultation and in a hospital-like setting.

Because of the potential for bleeding problems, patients should undergo pretreatment screening for bleeding disorders, including platelet function analyzer-100 (PFA-100) and platelet count.

As a general rule, drugs excreted by the kidney are eliminated twofold less efficiently when the GFR drops to 50 mL/min and thus may reach toxic levels at lower GFR. In these circumstances, drug dosage needs to be reduced and timing of administration must be prolonged. Nephrotoxic drugs such as acyclovir, aminoglycosides, aspirin, nonsteroidal anti-inflammatory drugs, and tetracycline require special dosage adjustments. Acetaminophen also is nephrotoxic and may cause renal tubular necrosis at high doses, but it is probably safer than aspirin in these patients because it is metabolized in the liver. Aspirin and nonsteroidal anti-inflammatory drugs potentiate uremic platelet defects; thus, these antiplatelet drugs should be avoided. Although nitrous oxide and diazepam are anti-anxiety drugs that require little modification for use in patients with ESRD, the hematocrit or hemoglobin concentration should be measured before intravenous sedation to ensure adequate oxygenation. Also, drugs that depress the central nervous system (barbiturates, narcotics) are best avoided in the presence of uremia because the blood–brain barrier may not be intact, and excessive sedation may result. When the hemoglobin concentration is below 10g/100mL, general anesthesia is not recommended for patients with ESRD.

Renal osteodystrophy following End-stage renal disease:



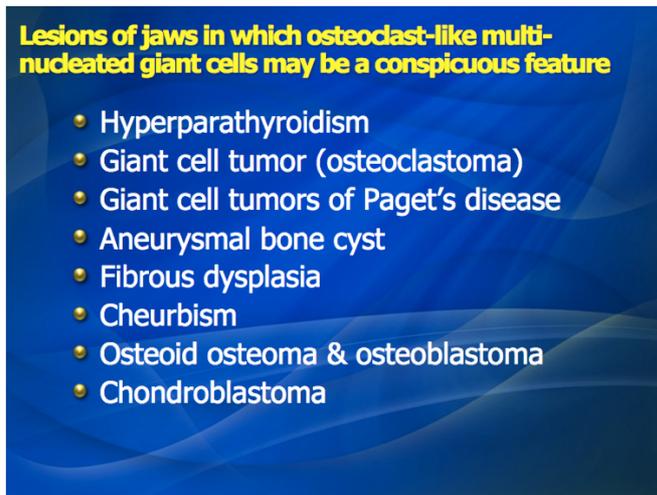
Specific osseous changes of the jaws accompany chronic renal failure. The most classically described osseous change is the triad of loss of lamina dura, demineralized bone (“ground glass”), and localized radiolucent jaw lesions (central giant cell granulomas; “brown tumor”). Lytic bone lesions are the result of hyperparathyroidism. Other osseous findings include widened trabeculations, loss of cortication, calcified extraction sites (“socket sclerosis”), and metastatic calcifications within the skull.

## Consideration in patients with renal disease:

As a class, the non-steroidal anti-inflammatory drugs are well known to have direct nephrotoxic effects. In a meta-analysis, hypertensive effect of NSAIDS was observed to be significant for patients with existing hypertension compared to those without hypertension. Depending on dietary salt intake adjustment, the mean systolic blood pressure increase was observed to be 3.6–6 mmHg for indomethacin and naproxen, but minimal or none for sulindac, aspirin and ibuprofen. In another meta-analysis, Johnson et al reported that the NSAIDS hypertensive effect was greater for patients receiving antihypertensive medications compared to those receiving placebo, 4.7 versus 1.8 mmHg, respectively, and greatest for those receiving  $\beta$ -blockers. In addition, among all commonly used NSAIDS included in the study, the greatest hypertensive effect was observed with piroxicam. Aspirin should be avoided in the chronic renal failure patient specially in  $GFR < 15$ . Ibuprofen does not need any dose adjustment in renal disease. Use of tetracycline is contraindicated in renal failure patients. Clindamycin does not need dose adjustment for these patients. Erythromycin is safe due to its liver metabolism.

Drug Adjustments in Chronic Renal Disease							
Drug	Route of Elimination in Metabolism	Removed by Dialysis	Dosage Adjustment for Renal Failure				Supplement Dose After Hemodialysis
			Method	GFR, mL/min			
				>50	Co-50	<10	
<b>ANALGESIC</b>							
Aspirin	Liver (kidney)	Yes	I	q4h	q6h	Avoid	Yes
Acetaminophen	Liver	Yes (HD); No (PD)	I	q4h	q6h	q8h	No
Ibuprofen (Motrin)	Liver	?	—	No adjustment			No
Propoxyphene* (Darvon)	Liver (kidney)	No	DR	100%	100%	Avoid	No
Codeine	Liver	?	DR	100%	75%	50%	No
Meperidine* (Demerol)	Liver	?	DR	100%	75%	50%	No
<b>ANESTHETIC</b>							
Lidocaine (Xylocaine)	Liver (kidney)	No	—	No adjustment			N/A
<b>ANTIMICROBIAL</b>							
Acyclovir (Zovirax)	Kidney	Yes	I & DR	q8h	q12-24h	50% q24-48h	Yes
Amoxicillin, Penicillin V	Kidney (liver)	No	I	q8h	q8-12h	q24h	Yes
Cephalexin (Keflex)	Kidney	Yes	I	q8h	q12h	q12h	Yes; 50% of usual dose after HD
Clindamycin (Cleocin)	Liver	No	—	100%	100%	100%	No
Erythromycin	Liver	No	DR	100%	100%	50%-75%	No
Ketoconazole (Nizoral)	Liver	No	—	100%	100%	100%	No
Metronidazole (Flagyl)	Liver (kidney)	Yes	DR	100%	100%	50%	Yes (HD); No (PD)
Tetracycline (Doxycycline)	Kidney (liver)	No	I	q8-12h	q12-24 <sup>h</sup>	q24h	No
<b>BENZODIAZEPINE</b>							
Diazepam (Valium); Triazolam (Halcion)	Liver	?	—	No adjustment			No
<b>CORTICOSTEROID</b>							
Dexamethasone	Local site and liver	—	—	No adjustment			No

Lesions that share the same characteristic of “Giant cell”.



### **3)Hepatic failure:**

Acetaminophen overdose (taking too much acetaminophen (Tylenol) is the most common cause of acute liver failure in the United States.

Many drugs commonly used in dentistry are metabolized principally by the liver; they may be used in patients with hepatic disease that is not severe, although in limited amounts. A quantity of three cartridges of 2% lidocaine (120 mg) is considered a relatively limited amount of drug.

Major categories of pain medications, including over-the-counter analgesics (OTCAs) such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as cyclooxygenase 2 (COX-2) inhibitors, anticonvulsants, antidepressants, and opioids, are largely metabolized by the liver.

In general, acetaminophen at reduced dosing is a safe option. In patients with cirrhosis, nonsteroidal anti-inflammatory drugs should be avoided to prevent renal failure, and opiates should be avoided or used sparingly, with low and infrequent dosing, to prevent encephalopathy.

Multiple hepatologists agree that 2 g or less per day of acetaminophen would be recommended for these patients (written communication, expert opinion). Careful follow-up of these patients is recommended.

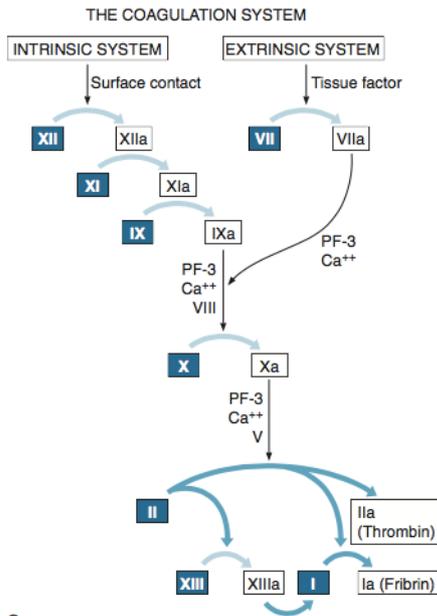
#### Dental Drugs Metabolized Primarily by the Liver

- Local anesthetics (appear safe for use during liver disease when used in appropriate amounts)
- Lidocaine (Xylocaine)
- Mepivacaine (Carbocaine)
- Prilocaine (Citanest)
- Bupivacaine (Marcaine)
- Analgesics
- Aspirin\*
- Acetaminophen (Tylenol, Datril)<sup>†</sup>
- Codeine<sup>†</sup>
- Meperidine (Demerol)<sup>†</sup>
- Ibuprofen (Motrin)\*
- Sedatives
- Diazepam (Valium)<sup>†</sup>
- Barbiturates<sup>†</sup>
- Antibiotics
- Ampicillin
- Tetracycline
- Metronidazole<sup>†</sup>
- Vancomycin<sup>†</sup>

### 3)Coagulation process, pathophysiology and dental management:

Platelets, blood proteins, lipids, and ions are involved in the process of coagulation. Thrombin is generated on the surface of the platelets, and bound fibrinogen is converted to fibrin. The end product of coagulation is a fibrin clot that can stop further blood loss from injured tissue. Prothrombin (factor II), factors VII, IX, and X, and proteins C, S, and Z are Vit K dependent

The intrinsic pathway is initiated by contact activation of factor XII. Coagulation proceeds through two pathways—the intrinsic and the extrinsic. Both use a common pathway to form the end-product, fibrin. The (faster) extrinsic pathway is initiated through tissue factor (an integral membrane protein) and is released or exposed through injury to tissues; this process activates factor VII (VIIa).



### Coagulation tests:

In the presence of liver disease, the production of coagulation factors I (fibrinogen), II (prothrombin), V, VII, VIII, IX, X, XI will be impaired. In this case, liver disease can affect both PT, PTT. Also, the platelet count will drop.

The prothrombin time (PT) along with international normalized ratio (INR) are assays evaluating the extrinsic pathway of coagulation. They are used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status. PT measures factors I (fibrinogen), II (prothrombin), V, VII, and X. It is used in conjunction with the activated partial thromboplastin time (aPTT) which measures the intrinsic pathway and common pathway. The use heparin can prolong the PTT.

A 2015 narrative review by Elad et al. specifically addressed the 4 currently marketed target-specific oral anticoagulants, providing a general overview and potential management strategies for dental practitioners. After consideration of factors such as patient comorbidity and the risk of bleeding from the procedure, and in addition to usual local measures to control bleeding (e.g., sutures, absorbable gelatin), the authors offered the following options for drug management:

1. continue regular dose administration of the anticoagulant;
2. postpone the timing of the daily dose of the anticoagulant (time the daily dose after the dental treatment or skip one daily dose); or time the dental intervention as late as possible after last dose of anticoagulant; or
3. temporarily interrupt drug therapy for 24 to 48 hours.

According to the authors, “Based on the current reported dental literature, limited dental surgery may benefit from the first 2 conservative options. However, this needs to be proven in comparative clinical trials.”

If the patient is taking aspirin or another platelet aggregation inhibitor: Excess bleeding is usually manageable through local measures only; discontinuation of medication is not recommended.

Patients on coumadin and aspirin with INR greater than 3.5 any invasive procedure such as I&D should be delayed until dosage is decreased. Physician will reduce patient’s dosage. Effect of reduced dosage takes 3-5 days. Meanwhile antibiotic with following considerations can be prescribed. Based on recent article (JADA) if INR 3.5-4.2, no modification of treatment needed even if patient required extraction or some surgical procedures

Drug interactions with warfarin:

DRUG CLASS	EFFECT ON WARFARIN/ MECHANISM	RECOMMENDATION/ COMMENTS
<b>Macrolides</b> Azithromycin ( <i>Zithromax</i> ) Clarithromycin ( <i>Biaxin</i> ) Erythromycin	Macrolides can <u>increase the effect</u> of warfarin through inhibition of hepatic metabolism of warfarin. <sup>2</sup> (Azithromycin affects warfarin by an unknown mechanism.)	<ul style="list-style-type: none"> <li>•Increased INR reported with all macrolides. Strongest evidence with erythromycin.<sup>2</sup> Increased INR reported with ophthalmic erythromycin.<sup>2f</sup></li> <li>•Monitor INR when any macrolide is started or stopped.<sup>a,b,c</sup></li> </ul>
<b>Metronidazole</b> ( <i>Flagyl</i> )	<u>Increased response</u> caused by inhibition of metabolism of warfarin. <sup>3</sup>	<ul style="list-style-type: none"> <li>•<b>Avoid use if possible.</b> Metronidazole can dramatically increase INR.<sup>25</sup> Topical preparations are less of a problem due to minimal systemic absorption.</li> <li>•If used, monitor INR closely when therapy started or stopped.<sup>a,b,c</sup> Some clinicians consider empirically lowering the warfarin dose by 25% to 40%.<sup>25</sup></li> </ul>
<b>Penicillins</b>	High doses of IV penicillins <u>increase</u> the risk of warfarin-associated bleeding by inhibiting platelet function. <sup>3</sup> Oral amoxicillin and amoxicillin/clavulanic acid may increase the risk of bleeding with warfarin. <sup>22,24</sup>  <b>Exception:</b> <u>Decreased response</u> seen with dicloxacillin and nafcillin possibly due to enhanced metabolism of warfarin. <sup>10</sup>	<ul style="list-style-type: none"> <li>•Oral penicillin G or V and ampicillin do not appear to interact with warfarin.<sup>2</sup></li> <li>•Monitor INR several days after start of dicloxacillin or nafcillin, and again after treatment ends. Effects might persist for weeks after dicloxacillin or nafcillin is discontinued.<sup>10,11</sup></li> <li>• For high-dose IV penicillins and amoxicillin or amoxicillin/clavulanic acid, monitor INR when therapy started or stopped.<sup>a,b,c</sup></li> </ul>

### **Von Willebrand's Disease:**

The most common inherited bleeding disorder is vWD, which is caused by an inherited defect involving platelet adhesion. Platelet adhesion is affected by a deficiency in vWF or a qualitative defect in the factor.

vWF binds factor VIII in circulating blood. Unbound factor VIII is destroyed in the circulation. Thus, variants of vWD with a significant reduction in vWF or with a vWF that is unable to bind factor VIII may show signs and symptoms of hemophilia A, in addition to those associated with defective platelet adhesion.

Laboratory investigation is needed to make the diagnosis. Screening laboratory tests may show prolonged PFA-100, prolonged aPTT, normal platelet count, normal PT, and normal TT. Additional laboratory tests are needed to establish the diagnosis and type of vWD.

Patients with type 1 vWD are the best candidates for desmopressin therapy. Desmopressin (DDAVP) stimulates the release of von Willebrand factor (vWF) from the endothelial cells, thereby increasing the levels of Vwf. Desmopressin can be used to promote the release of von Willebrand factor (with subsequent increase in factor VIII survival secondary to vWF complexing) in patients with coagulation disorders such as von Willebrand disease.

### **4) Infective endocarditis (IE):**

IE is a microbial infection of the endothelial surface of the heart or heart valves that most often occurs in proximity to congenital or acquired cardiac defects. A total of 80% to 90% of cases of identified IE are due to streptococci viridans alpha hemolytic due to their chemotaxis for heart valves. This variation depends on the type of valve infected (i.e., native or prosthetic), whether the infection is community acquired or hospital acquired (nosocomial), and whether or not the patient is an IVDU. Streptococci continue to be the most common cause of IE, but staphylococci have been gaining increasing importance. The mechanism is thought to be the result of a series of complex interactions of several factors involving endothelium, bacteria, and the host immune response. The classic findings of IE include fever, heart murmur, and positive blood culture, although the clinical presentation may be varied. It is of particular significance that the interval between the presumed initiating bacteremia and the onset of symptoms of IE is estimated to be less than 2 weeks in more than 80% of patients with IE. If the IE presents more than 2 weeks after dental appointment it is very unlikely that dental app is the initiating factor. Fever, the most common sign of IE, occurs in up to 95% of patients. The management of patients with IE requires effective antibiotic therapy and, for cases with significant structural damage, cardiac or surgical intervention.

**Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis for Which Prophylaxis With Dental Procedures Is Recommended**

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD)<sup>†</sup>
  - Unrepaired cyanotic CHD, including those with palliative shunts and conduits
  - Completely repaired CHD with prosthetic material or device by surgery or catheter intervention during the first 6 months after the procedure\*
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device, which inhibits endothelialization
- Cardiac transplantation recipients who develop cardiac valvulopathy

**Dental Procedures for Which Endocarditis Prophylaxis Is Recommended for Patients in Box 2-1**

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
- This includes all dental procedures except the following procedures and events:
  - Routine anesthetic injections through noninfected tissue
  - Taking of dental radiographs
  - Placement of removable prosthodontic or orthodontic appliances
  - Adjustment of orthodontic appliances
  - Shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa

Situation	Agent	Regimen: Single Dose 30-60 Minutes before Procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin or Cefazolin or Ceftriaxone	2 g IM or IV	50 mg/kg IM or IV
		1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin (oral)	Cephalexin <sup>†</sup> or Clindamycin	2 g	50 mg/kg
		600 mg	20 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Azithromycin or Clarithromycin	500 mg	15 mg/kg
	Cefazolin or Ceftriaxone <sup>†</sup>	1 g IM or IV	50 mg/kg
	Clindamycin phosphate	600 mg IM or IV	20 mg/kg IM or IV

If the patient is allergic to penicillin and already taking clindamycin for another reason, azithromycin will be the antibiotic of choice.

In a new study by siqueira et al (JOE, 2016) it was reported that no detectable bacteremia was evident by culture after treatment of infected root canals. Molecular analysis revealed bacterial DNA and streptococci in blood from some patients without

a significant difference between individuals receiving or not receiving antibiotic prophylaxis.

### **5) Joint replacement need antibiotic prophylaxis:**

In patients with prosthetic joint implants, a 2017 ADA clinical practice guideline, based on a 2014 systematic review states, "In general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended prior to dental procedures to prevent prosthetic joint infection."

"The new CSA guideline clearly states that for most patients, prophylactic antibiotics are not indicated before dental procedures to prevent [prosthetic joint infections]. The new guideline also takes into consideration that patients who have previous medical conditions or complications associated with their joint replacement surgery may have specific needs calling for premedication. In medically compromised patients who are undergoing dental procedures that include gingival manipulation or mucosal inclusion, prophylactic antibiotics should be considered only after consultation with the patient and orthopedic surgeon. For patients with serious health conditions, such as immunocompromising diseases, it may be appropriate for the orthopedic surgeon to recommend an antibiotic regimen when medically indicated, as footnoted in the new chair-side guide."

### **6) CD4 count and progression of infection:**

Above 500 CD4 cells no unusual infections are likely to occur. 200-500 CD4 cells there is an increased risk for certain infections, such as shingles, thrush, skin infections, bacterial sinus and lung infections, and TB. <200 CD4 cells there is an increased risk for PCP (pneumonia), and you should begin treatment to prevent it.

If the neutrophil count in a patient is <500 cells/mm, if the WBC<2000 the oral health care provider should administer antibiotics pre-operatively and post-operatively in consultation with the primary care provider. An individual assessment of risk related to the patient's condition and type of surgery should be performed. All HIV-related infections and malignancies escalate in frequency and morbidity as the absolute CD4 T-lymphocyte count falls toward 200 cells/ $\mu$ L and below. Therefore, the CD4 count must be current to within 4 months to determine the risk of infection in a specific patient and serve as an impetus to drug prophylaxis or other interventions. Patients should be aware of their CD4 count and their risk of specific infections.

When the CD4 count drops below 200 due to advanced HIV disease, a person is diagnosed with AIDS.

## **7)Rheumatoid arthritis (RA):**

RA is an autoimmune disease of unknown origin that is characterized by symmetric inflammation of joints, especially of the hands, feet, and knees. The cause of RA is unknown; however, evidence seems to implicate an interrelationship of infectious agents, genetics, and autoimmunity. With RA, the fundamental abnormality involves micro-vascular endothelial cell activation and injury. Primary changes occur within the synovium, which is the inner lining of the joint capsule. Edema of the synovium occurs, followed by thickening and folding. This excessive tissue, composed of proliferative and invasive granulation tissue, is referred to as pannus. In addition, marked infiltration of lymphocytes and plasma cells into the capsule occurs. Eventually, granulation tissue covers the articular surfaces and destroys the cartilage and subchondral bone through enzymatic activity.

A likely sequence of events begins with a synovitis that stimulates immunoglobulin G (IgG) antibodies. These antibodies form antigenic aggregates in the joint space, leading to the production of rheumatoid factor (hypersensitivity type III, autoantibodies). Rheumatoid factor then complexes with IgG, complement, a process that produces an inflammatory reaction that injures the joint space.

In comparison to arthritis, RA might not be painful due to its autoimmune nature. Laboratory findings most commonly seen in RA include an increased erythrocyte sedimentation rate, the presence of C-reactive protein, a positive rheumatoid factor in 85% of affected patients, and a hypochromic/microcytic anemia.

Treatment goals are to reduce joint inflammation and swelling, relieve pain and stiffness, and facilitate and encourage normal function. These goals are accomplished through a basic treatment program that consists of patient education, rest, exercise, physical therapy, and aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

The most significant complication of the oral and maxillofacial complex in RA is TMJ involvement, which is found in up to 45% to 75% of patients with RA. This may present as bilateral preauricular pain, tenderness, swelling, stiffness, and decreased mobility of the TMJ, or it may be asymptomatic.

## **8) Systemic lupus erythematosus (SLE):**

Systemic Lupus is a prototypical autoimmune disease that predominantly affects women of childbearing age, with a female/ male ratio of 5:1. SLE is an autoimmune disease. The production of pathogenic antibodies and immune complexes and their deposition with resultant inflammation and vasculopathy is the basic abnormality that underlies SLE. Clinical expression of the disease reflects the organs or tissues involved and the extent of that involvement. Patients who are diagnosed with Lupus are more likely to be diagnosed with other autoimmune connective tissue disorders like RF.

Because of the widespread systemic involvement of SLE, multiple manifestations are observed in many tissues and organs. Although malaise, overwhelming fatigue, fever, and weight loss are nonspecific manifestations that affect most patients at some time in their disease course, the classic picture of SLE is that of a young woman with polyarthritis and a butterfly-shaped rash across the nose and cheeks. Arthritis, the most common manifestation of SLE, is seen in as many as 76% of patients. It affects the small joints and is migratory, and the pain typically is out of proportion to the signs. The classic butterfly rash of the nose and cheeks is found in only about one third of patients with SLE.

The antinuclear antibody test is the best screening test for SLE because it is positive in 95% of patients. This positivity also occurs in patients with other rheumatic diseases. Anti-DNA assays—double helix and single helix—also are elevated in 65% to 80% of patients with active untreated SLE

No specific treatment planning modifications are required. However, consideration should be given to physical disabilities related to arthritis and myalgia. Additionally, systemic complications such as renal impairment and cardiac problems such as arrhythmia and valvar defects may occur. For patients with SLE, the establishment and maintenance of optimal oral health are of paramount importance.

Approximately 4% of patients had cardiac valve abnormalities that placed them in the moderate risk group for endocarditis. However, no cases demonstrated a relationship between endocarditis and SLE. On the basis of 2007 American Heart Association guidelines, none of these patients are recommended for antibiotic prophylaxis for invasive dental procedures.

### Dental Management of Patient With Systemic Lupus Erythematosus

#### KEY POINTS

1. Consultation with physician
  - a. Patient status and stability
  - b. Extent of systemic manifestations (i.e., kidney, heart)
  - c. Hematologic profile (complete blood cell count [CBC] with differential, prothrombin time [PT], partial thromboplastin time [PTT], bleeding time [BT])
  - d. Drug profile
2. Drug considerations
  - a. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)—bleeding may be increased but is not usually clinically significant; if patient is concurrently taking corticosteroids, bleeding is more likely—suggest obtaining pretreatment bleeding time (<20 minutes)
  - b. Gold salts, antimalarials, penicillamine, and cytotoxic drugs may cause leukopenia and thrombocytopenia; also, severe stomatitis—treat symptomatically
  - c. Corticosteroids may cause adrenal suppression
3. Hematologic considerations
  - a. Leukopenia with corticosteroids or cytotoxic drugs may predispose patient to infection; use of postoperative antibiotics can be considered with surgical procedures
  - b. Platelet count <50,000/mm<sup>3</sup> may result in severe bleeding—consultation with physician
  - c. Elevated PTT associated with lupus anticoagulant usually does not cause increased bleeding—surgery can be performed
4. Infective endocarditis is a potential problem—antibiotic prophylaxis is not recommended by the American Heart Association.

## 9)Raynaud's phenomenon:

Raynaud's disease or Raynaud's phenomenon is excessively reduced blood flow in response to cold or emotional stress, causing discoloration of the fingers, toes, and occasionally other areas. This condition may also cause nails to become brittle with longitudinal ridges. The phenomenon is believed to be the result of vasospasms that decrease blood supply to the respective regions. When the disorder's cause is idiopathic, it is referred to as Raynaud's disease (also called primary Raynaud's); if the syndrome is secondary to another disease such as systemic sclerosis, Scleroderma, or other connective tissue disorders, it is correctly referred to as Raynaud's phenomenon (secondary Raynaud's). Secondary Raynaud's has a number of associations: Connective tissue disorders: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome.

## 10) Scleroderma:

Scleroderma is a long term autoimmune disease that results in hardening of the skin. It is characterized by increased synthesis of collagen (leading to the sclerosis), damage to small blood vessels, activation of T lymphocytes and production of altered connective tissues. One of the dental signs is generalized widening of the PDL.

## 11) Dental management of patients undergoing chemotherapy/radiotherapy:

If head and neck radiation and immunosuppressive chemotherapy are scheduled, the following recommendations should be considered:

Non-restorable teeth with poor or hopeless prognosis, acute infection, or severe periodontal disease that may predispose the patient to complications (e.g., sepsis, osteoradionecrosis) should be extracted; sharp, bony edges trimmed and smoothed; and primary closure obtained. Chronic inflammatory lesions in the jaws and potential sources of infection should be examined and treated or eradicated before radiation or chemotherapy.

Adequate time for wound healing should be provided for extractions and surgical procedures before radiation therapy or myelosuppressive chemotherapy is induced.

Symptomatic nonvital teeth should be endodontically treated at least 1 week before initiation of head and neck radiation or chemotherapy. However, dental treatment of asymptomatic teeth even with periapical involvement may be delayed.

One should prioritize treatment of infections and extractions, periodontal care, and treatment of irritations before providing treatment of carious teeth, root canal therapy, and replacement of faulty restorations. Temporary restorations may be placed and some types of treatment (e.g., cosmetic, prosthodontic, endodontic) can be delayed when time is limited.

### Guidelines for Tooth Extraction in Patients Scheduled to Receive Radiation Treatment to the Head and Neck (Including the Mouth) or Chemotherapy

#### INDICATORS OF EXTRACTION

- Pocket depths are 6 mm or greater, mobility is excessive, purulence is seen on probing
- Periapical inflammation is noted
- Tooth is broken down, nonrestorable, nonfunctional, or partially erupted; patient is noncompliant with oral hygiene measures
- Patient has no interest in saving tooth/teeth
- Tooth is associated with an inflammatory (e.g., pericoronitis), infectious, or malignant osseous disease

#### EXTRACTION GUIDELINES

- Perform extraction with minimal trauma
  - At least 2 weeks before initiation of radiation therapy\*

- Ideally 3 weeks before initiation of radiation therapy
- At least 5 days (in maxilla) before initiation of chemotherapy
- At least 7 days (in mandible) before initiation of chemotherapy
- Trim bone at wound margins to eliminate sharp edges
- Obtain primary closure
- Avoid intra-alveolar hemostatic packing agents that can serve as a nidus of microbial growth
- Transfuse if the platelet count is less than 50,000/mm<sup>3</sup>
- Delay if the white blood count is less than 2000/mm<sup>3</sup> or the absolute neutrophil is less than 1000/mm<sup>3</sup> or is expected to be this level within 10 days; alternatively, prophylactic antibiotics (cephalosporin) may be used with extractions that are mandatory

## **12)Osteoradionecrosis (ORN):**

ORN is a condition that is characterized by exposed bone that fails to heal (present for 6 months) after high-dose radiation to the jaws. ORN results from radiation-induced changes (hypocellularity, hypovascularity, and ischemia) in the jaws. Most cases result from damage to tissues overlying the bone rather than from direct damage to the bone. Accordingly, soft tissue necrosis usually precedes ORN and is variably present at the time of diagnosis. Risk is greatest in posterior mandibular sites for patients whose jaws have been treated with in excess of 6500 cGy, who continue to smoke, and who have undergone a traumatic (e.g., extraction) procedure. Risk is greater for dentate patients than for edentulous patients, and periodontal disease enhances risk. Nonsurgical procedures that are traumatic (e.g., curettage) or that cause a reduction in blood supply to the region (e.g., use of vasoconstrictors) can result in ORN.

If the dentist is unsure of the amount of radiation that was received and if invasive procedures are planned, the radiation oncologist should be contacted to determine the total dose given to the head and neck region before care is initiated. Clinicians should be aware that risk of ORN increases with increasing dose to the jaws (e.g., 7500 cGy presents a greater risk than 6500 cGy). Patients determined to be at risk should be provided appropriate preventive measures. Protocols to reduce the risk of ORN include selection of endodontic therapy over extraction, use of nonlidocaine local anesthetics that contain no or low concentrations of epinephrine, atraumatic surgical procedures (if surgery is necessary), prophylactic antibiotics plus antibiotics during the week of healing (penicillin VK for 7 days), and hyperbaric oxygen administered before invasive procedures are performed

reduction in blood flow after radiotherapy is much greater in the mandible than in the maxilla. Therefore, mandible is at greater risk for developing necrosis (AAE colleagues for excellence)

## **Endodontic Implications of Bisphosphonate-Associated Osteonecrosis of the Jaws:**

Bisphosphonates are commonly used to treat certain resorptive bone diseases such as osteoporosis, Paget's disease and hypercalcemia associated with certain malignancies such as multiple myeloma and bone metastasis from the breast or prostate. Bisphosphonates inhibit bone resorption by inhibiting osteoclast activity. There is growing recognition that bisphosphonates may be associated with a rare adverse event called osteonecrosis of the jaws

Patients presenting with bisphosphonate-associated ONJ typically present with an irregular mucosal ulceration with exposed bone in the mandible or maxilla and pain or swelling in the affected jaw.

Common risk factors associated with the development of bisphosphonate-associated ONJ include: • History of taking bisphosphonates, especially I.V. formulations. The concurrent use of steroids appears to contribute to this risk. • Previous history of cancer (e.g., multiple myeloma or metastatic disease to bone), osteoporosis, Paget's disease or other indications for bisphosphonate treatment. • A history of a traumatic dental procedure. Patients receiving high dose I.V. bisphosphonates for greater than two years are most at risk for developing osteonecrosis of the jaw. The estimated risk ranges from 0.8% to 20% in these patients. The higher the bisphosphonate dose and the longer the exposure time, the more likely that osteonecrosis will develop.

Preventive care might include caries control, conservative periodontal and restorative treatments, and, if necessary, appropriate endodontic treatment. Similar to the management of the patient with osteoradionecrosis, management of high risk patients might include nonsurgical endodontic treatment of teeth that otherwise would be extracted. Teeth with extensive carious lesions might be treated by nonsurgical endodontic therapy possibly followed by crown resection and restoration similar to preparing an overdenture abutment. Surgical procedures such as tooth extractions, endodontic surgical procedures or placement of dental implants should be avoided if possible.

### **13) Asthma:**

Chronic inflammatory respiratory disease that is associated with increased airway hyperresponsiveness. Typical symptoms of asthma consist of reversible episodes of breathlessness (dyspnea), wheezing, cough that is worse at night, chest tightness, and flushing. Onset usually is sudden, with peak symptoms occurring within 10 to 15 minutes. The difference between asthma attack and when something caught in trachea is that patients with asthma can talk.

Allergic or extrinsic asthma is the most common form. Allergic asthma is usually seen in children and young adults. In these patients, a dose- response relationship exists between allergen exposure and immunoglobulin E (IgE)-mediated sensitization, positive skin testing to various allergens, and associated family history of allergic disease. Inflammatory responses are mediated primarily by type 2 helper T ( $T_H2$ ) cells that secrete interleukins (IL-4) and stimulate B cells to produce IgE. During an attack, allergens interact with IgE antibodies affixed to mast cells, basophils, and eosinophils along the tracheobronchial tree. The complex of antigen with antibody causes leukocytes to degranulate and secrete vasoactive autocooids and cytokines such as bradykinins, histamine, leukotrienes, and prostaglandins. Histamine and leukotrienes cause smooth muscle contraction (bronchoconstriction) and increased vascular

permeability, and they attract eosinophils into the airway. The release of platelet-activating factor sustains bronchial hyperresponsiveness. T lymphocytes prolong the inflammatory response (late phase response), and imbalances in matrix metalloproteinases and tissue inhibitor metalloproteinases may contribute to fibrotic changes.

current guidelines recommend a “step care” approach with the use of inhaled anti-inflammatory agents (first tier: corticosteroids; alternatives: leukotriene inhibitors) for the prophylaxis of chronic asthma. Beta 2-adrenergic agonists and anticholinergic drugs are secondary agents that should be added (i.e., not to be used alone) when anti-inflammatory drugs are inadequate. Anti-leukotrienes are most useful in mild to moderate asthma and in blocking aspirin-induced asthmatic responses.

The goal of management for dental patients with asthma must be to prevent an acute asthma attack. The first step in achieving this goal is to identify patients with asthma by history, learn as much as possible about their problem, and prevent precipitating factors. Patients should be instructed to regularly use their medications, bring their inhalers (bronchodilators) to each appointment, and inform the dentist at the earliest sign or symptom of an asthma attack. Prophylactic inhalation of a patient’s bronchodilator at the beginning of the appointment is a valuable method of preventing an asthma attack.

If sedation is required, nitrous oxide/oxygen inhalation is best. Nitrous oxide is not a respiratory depressant, nor is it an irritant to the tracheobronchial tree. Barbiturates and narcotics, particularly meperidine, are histamine-releasing drugs that can provoke an attack and should be avoided.

For emergency in dental office, administer fast-acting bronchodilator (NOTE: Corticosteroids have delayed onset of action), oxygen, and, if needed, subcutaneous 0.3 to 0.5 ml of epinephrine (1:1000) and repeat administration of fast-acting bronchodilator every 5 minutes until EMS arrives

#### Dental Management of the Patient With Asthma

1. Identify and assess by history
  - Type of asthma (mild, moderate, or severe)
  - Precipitating factors (and plan for allergen avoidance)
  - Age at onset
  - Level of control (frequency, time of day, and severity of attacks)
    - How usually managed
    - Medications being taken (how often quick-relief medication is used) and taken correctly on the day of the appointment
    - Necessity of emergency care (life-threatening attacks, hospitalizations, emergency department visits)
    - Baseline forced expiratory volume in 1 second (FEV<sub>1</sub>) stable (not decreasing)
2. Avoid known precipitating factors
3. Obtain medical consultation for patient with severe persistent asthma
4. Ask patient to bring current medication inhaler to every appointment and to keep it available; (used prophylactically in persons with moderate to severe persistent disease)
5. Drug considerations
  - Avoid aspirin-containing medications (use acetaminophen)
  - Avoid nonsteroidal antiinflammatory drugs (NSAIDs) (see Table 16-3)
  - Avoid barbiturates and narcotics (histamine-releasing drugs)
  - Avoid erythromycin and macrolide antibiotics in patients taking theophylline
  - Discontinue cimetidine 24 hr before intravenous sedation in patients taking theophylline
6. Local anesthetic considerations (may elect to avoid solutions containing epinephrine or levonordefrin because of sulfite preservative)
7. Patients taking chronic corticosteroid medications over the long term may require supplementation (see Chapter 16)
8. Provide stress-free environment through establishment of rapport and openness
9. If sedation is required, nitrous oxide/oxygen inhalation sedation and/or small doses of oral diazepam recommended
10. Recognize signs and symptoms of a severe or worsening asthma attack
  - Inability to finish sentences with one breath
  - Ineffectiveness of bronchodilators to relieve dyspnea
  - Tachypnea equal to or greater than 25 breaths per minute
  - Tachycardia equal to or greater than 110 beats per minute
  - Diaphoresis
  - Accessory muscle usage
  - Paradoxical pulse
11. Administer fast-acting bronchodilator (NOTE: Corticosteroids have delayed onset of action), oxygen, and, if needed, subcutaneous 0.3 to 0.5 mL of epinephrine (1:1000)
12. Activate emergency medical system (EMS)
13. Repeat administration of fast-acting bronchodilator every 5 minutes until EMS arrives

**Theophylline** is a xanthine derivative that acts as a bronchodilator by directly relaxing smooth muscle of the bronchial airways and pulmonary blood vessels.

Therapeutic Effect: Relieves bronchospasm and increases vital capacity.

Increased action: erythromycin (macrolides), the use of Theophylline and macrolides is contraindicated.

#### **14)Dental management of patients with Parkinson and possible drug interaction:**

Parkinson's disease is caused by death and depletion of dopaminergic neurons, which are manufactured in the substantia nigra and released in the caudate nucleus and putamen (the nigrostriatal pathway).

No adverse interactions have been reported between COMT inhibitors (A COMT inhibitor is a drug that inhibits the action of catechol-O-methyl transferase. This enzyme is involved in degrading neurotransmitters. COMT inhibitors are used in the treatment of Parkinson's disease) and epinephrine at dosages typically used in dentistry, they can potentially interact, and it is advisable to limit the dose of epinephrine to 2 carpules containing 1:100,000 epinephrine (36 µg) in patients who take COMT inhibitors. Erythromycin should not be given to patients who take the dopamine agonist, pramipexole (Mirapex). The clinician should be aware that antiparkinsonian drugs can be CNS depressants, and a dentally prescribed sedative may have an additive effect.

## **15) Seizure and benzodiazepines:**

Benzodiazepines work by increasing the efficiency of a natural brain chemical, GABA, to decrease the excitability of neurons. This reduces the communication between neurons and, therefore, has a calming effect on many of the functions of the brain. GABA controls the excitability of neurons by binding to the GABA-A receptor. The GABA-A receptor is a protein complex located in the synapses of neurons. All GABA-A receptors contain an ion channel that conducts chloride ions across neuronal cell membranes and two binding sites for the neurotransmitter gamma-aminobutyric acid (GABA), while a subset of GABA-A receptor complexes also contain a single binding site for benzodiazepines. This group of drugs results in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties.

\*Midazolam, is a short acting, water soluble benzodiazepine that can be administered IM and it doesn't need IV access. As opposed to diazepam (valium) which is soluble in lipid and need IV access. Sublingual triazolam for the provision of anxiolytics in the dental setting. It has been concluded that sublingual triazolam results in greater anxiolytic activity and less pain perception than oral administration as a result of greater plasma drug levels and may be useful as an alternative for nonparenteral outpatient sedation. Flumazenil is of benefit in patients who become excessively drowsy after benzodiazepines (Triazolam, Diazepam) are used for either diagnostic or therapeutic procedures. It has been used as an antidote in the treatment of benzodiazepine overdoses. It reverses the effects of benzodiazepines by competitive inhibition at the benzodiazepine binding site on the GABA-A receptor.

\*Phenytoin is an anticonvulsant drug that can stabilize neuronal membranes and decreases seizure activity by increasing efflux or decreasing influx of sodium ions across cell membranes from neurons of the motor cortex. Phenytoin may increase cardiac depressant effects of lidocaine and propranolol. This interaction should be considered for patients currently under active treatment.

## **16) Anti-depressant drugs and dental management:**

MAOIs were the first class of anti-depressants to be developed. They fell out of favor because of concerns about interactions with certain foods and numerous drug interactions. MAOIs elevate the levels of norepinephrine, serotonin, and dopamine by inhibiting an enzyme called monoamine oxidase. Monoamine oxidase breaks down norepinephrine, serotonin, and dopamine. When monoamine oxidase is inhibited, norepinephrine, serotonin, and dopamine are not broken down, increasing the concentration of all three neurotransmitters in the brain. They are also used for treating

Parkinson's. These class of drugs should be administrated carefully with SSRI and epi containing drugs like local anesthesia. Patients who are taking MAO inhibitors can receive small amounts of epinephrine in local anesthetics. Other forms of epinephrine (retraction cord, topical for control of bleeding) are best avoided. Phenylephrine must not be used in patients who are taking MAO inhibitors. Linezolid antibiotic can cause serotonin syndrome if combined with MAOIs.

### **17)Myasthenia gravis (MG):**

MG is a chronic autoimmune neuromuscular disease which is associated with muscular weakness and fatigue. MG, may be associated with an antibody-mediated autoimmune attack directed toward the acetylcholine receptors at the neuromuscular junctions. Autoantibodies reduce the availability of the target antigen, the nicotinic acetylcholine receptors. This results in an unusually limited duration of the neural impulses and small amplitude of the motor unit potential. Amide-type local anesthetics, such as lidocaine (Xylocaine) or mepivacaine (Carbocaine), can be administered safely. Local anesthetics administered using the intraligamentary or intrapulpal techniques should be considered to minimize doses of the drugs when possible. Use of tylenon, penicillin and NSAIDs are safe in these patients.

### **18)Diabetic patients:**

The glycosylated hemoglobin value (HbA1c) is the primary target for glycemic control. The American Diabetes Association recommends that the blood test—which measures average levels of glycemia over the preceding 2 to 3 months—should be performed at least twice a year in patients whose treatment goals are being met (and who have stable glycemic control), and quarterly in patients whose treatment has changed or whose goals are not being met. The goal for patients in general is an HbA1c value of less than 7%, and the goal for each individual patient is as close to normal (less than 6%) as is possible without the occurrence of clinically significant hypoglycemia.

### Dental Management of the Patient With Diabetes\*

1. Non-insulin-dependent patient:  
If diabetes is well-controlled,<sup>†</sup> all dental procedures can be performed without special precautions.
2. Insulin-controlled patient:
  - If diabetes is well-controlled,<sup>†</sup> all dental procedures can be performed without special precautions.
  - Morning appointments are usually best.
  - Patient advised to take usual insulin dosage and normal meals on day of dental appointment; information confirmed when patient comes for appointment.
  - Advise patient to inform dentist or staff if symptoms of insulin reaction occur during dental visit.
  - Glucose source (orange juice, soda, Glucola) should be available and given to the patient if symptoms of insulin reaction occur.
3. If extensive surgery is needed:
  - Consult with patient's physician concerning dietary needs during postoperative period.
  - Antibiotic prophylaxis can be considered for patients with brittle diabetes and those taking high doses of insulin who also have chronic states of oral infection.

If not well-controlled (i.e., does not meet ANY of above criteria: fasting blood glucose <70 mg/dL or >200 mg/dL and ANY complications [post MI, renal disease, congestive heart failure, symptomatic angina, old age, cardiac dysrhythmia, cerebrovascular accident], and blood pressure ≥180/110 mm Hg, or functional capacity <4 metabolic equivalents):

- Provide appropriate emergency care only.
- Request referral for medical evaluation, management, and risk factor modification
  - If symptomatic, seek IMMEDIATE referral
  - If asymptomatic, request routine referral

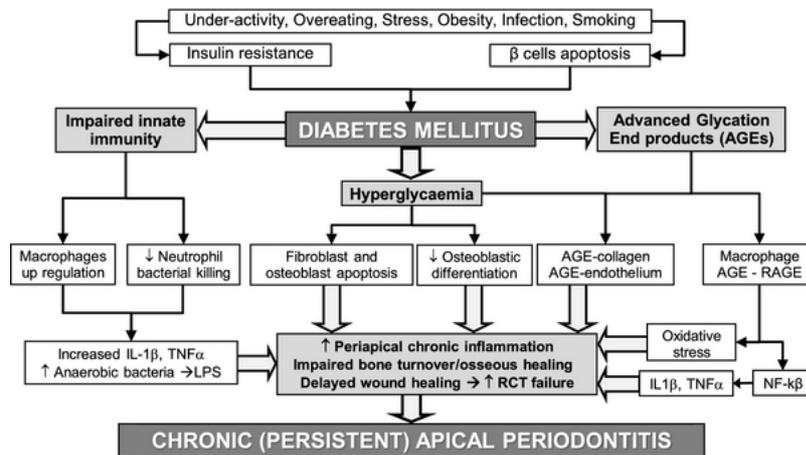
### Comparison of type 1 and 2 diabetates:

	Type 1	Type 2
Frequency, % of person with diabetes	5-10	90-95
Age at onset, y	15	40 and over
Body build	Normal or thin	Obese
Severity	Extreme	Mild
Insulin	Almost all	25% to 30%
Plasma glucagons	High, suppressible	High, resistant
Oral hypoglycemic agents	Few respond	50% respond
Ketoacidosis	Common	Uncommon
Complications	90% in 20 years	Less common
Rate of clinical onset	Rapid	Slow
Stability	Unstable	Stable
Genetic locus	Chromosome 6	Chromosome 11(?)
HLA and abnormal autoimmune reactions	Present	Not present
Insulin receptor defects	Usually not found	Often found

Ketoacidosis is a type of diabetic coma which is more common in type 1. It is due to over production of ketone bodies due to inability in burning glucose. It is a chronic condition and does not develop in one day. However, insulin shock is a consequence of too much insulin intake and it is an acute and sudden.

## The effect of diabetes and ketoacidosis on the immune system:

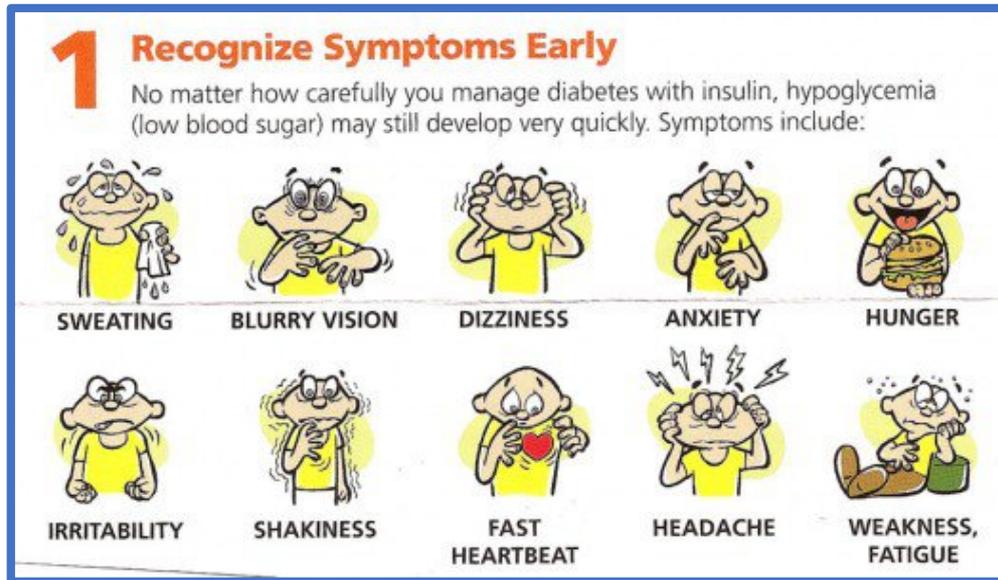
Uncontrolled diabetes can impair PMN Protein fragment transfer across membrane. It also affects bone coupling and healing



## Diabetic patients and antibiotic premedication:

Patients who have brittle diabetes (very difficult to control) or who require a high dosage of insulin (type 1 diabetes) may be at increased risk for postoperative infection. However, prophylactic antibiotics usually are not indicated. If the patient develops an infection, appropriate systemic antibiotics may be given. A protocol for IV sedation often involves fasting before the appointment (i.e., nothing by mouth after midnight); using only half the usual insulin dose; and then supplementing with IV glucose during the procedure. Patients with well-controlled diabetes may be given general anesthesia, if necessary; however, in a dental office, management with local anesthetics is preferable. The risk for infection in patients with diabetes is directly related to fasting blood glucose levels. If fasting blood glucose level is below 206 mg/100 mL, no increased risk is present; however, if fasting blood glucose level is between 207 and 229 mg/100 mL, the risk is increased by 20%. Additionally, if fasting blood glucose level rises to above 230 mg/100 mL, an 80% increase has occurred in the risk of infection. Therefore, dentists must be aware of the level of glycemic control in patients undergoing complex oral surgical procedures.

## Managing patients with hypoglycemia:



## 19) Tuberculosis and dental management:

M. tuberculosis replication leads to a host inflammatory and granulomatous response (hyper-responsivity type 4) and classic pulmonary and systemic symptoms. M. tuberculosis is typically transmitted by way of infected airborne droplets of mucus or saliva that are forcefully expelled from the lungs, most commonly through coughing but also by sneezing and talking.

At approximately 2 to 8 weeks after onset of infection, delayed hypersensitivity (type IV) to the bacteria develops that is mediated by T (CD4) helper lymphocytes. This condition manifests as conversion of the tuberculin skin test (purified protein derivative [PPD]) from negative to positive. Subsequently, a chronic granulomatous inflammatory reaction develops that involves activated epithelioid macrophages and formation of granulomas. These natural host defenses usually control and contain the primary pulmonary TB infection, resulting in latent tuberculosis infection. If not contained, the nidus of infection (granuloma) may become a productive tubercle with central necrosis and caseation.

When TB is managed, decisions regarding care are based on the potential infectivity of the patient. The four infectivity categories consist of (1) active TB, (2) a history of TB, (3) a positive tuberculin test, and (4) signs or symptoms suggestive of TB

## Dental Management of the Patient With a History of Tuberculosis

1. Active sputum-positive tuberculosis
  - Consult with physician before treatment
  - Perform urgent care only; palliate urgent problems with medication if contained facility in a hospital environment is not available
  - Perform urgent care that requires the use of a handpiece (older than 6 years) only in a hospital setting with isolation, sterilization (gloves, mask, gown), and special ventilation
  - Treat those under the age of 6 years as normal patients (noninfectious after consultation with physician to verify status)
  - Treat the patient who produces consistently negative sputum as a normal patient (noninfectious—verify with physician)
2. History of tuberculosis
  - Approach with caution, obtain good history of disease and its treatment duration, make appropriate review of systems mandatory
  - Obtain from patient a history of periodic chest radiographs and physical examination to rule out reactivation or relapse
  - Consult with physician and postpone treatment if there is:
    - Questionable history of adequate treatment time
    - Lack of appropriate medical follow-up since recovery
    - Sign or symptom of relapse
  - Treat as normal patient if present status is free of clinically active disease
3. Recent conversion to positive tuberculin skin test
  - Verify if evaluated by physician to rule out active disease
  - Verify if receiving isoniazid for 6 months to 1 year for prophylaxis
  - Treat as a normal patient
4. Signs or symptoms suggestive of tuberculosis
  - Refer to physician and postpone treatment
  - Treat as in 1 above if treatment is necessary

Isoniazid, rifampin, and pyrazinamide therapy may cause hepatotoxicity and elevations in serum aminotransferases. Rifampin induces cytochrome P450 enzymes. As a result, the use of rifampin can lower plasma levels of oral contraceptives, diazepam, clarithromycin, ketoconazole, itraconazole, and fluconazole. In addition, rifampin can cause leukopenia, hemolytic anemia, and thrombocytopenia, resulting in an increased incidence of infection, delayed healing, and gingival bleeding. Nonsteroidal anti-inflammatory drugs should be avoided in patients taking fluoroquinolones (second-line antituberculosis drugs) because of adverse central nervous system effects such as dizziness, insomnia, headache, or psychosis.

## **20)Adrenal gland pathology and dental management:**

Disorders that affect the adrenal glands result in overproduction or underproduction of adrenal products. Excess production of the adrenal glands results in the over- production of cortisol, mineralocorticoids, androgens, or estrogen, in isolation or combination. The most common type of overproduction is due to glucocorticoid excess and, when caused by pathophysiologic processes, is known as Cushing's disease.

Insufficient adrenocortical function may occur primarily or secondarily. Primary adrenocortical insufficiency is uncommon and is known as Addison's disease. The more common form, secondary adrenocortical insufficiency, results from hypothalamic or pituitary disease or from the administration of exogenous corticosteroids.

**1. Addison's disease** is caused by the lack of these compounds. Lack of cortisol results in impaired metabolism of glucose, fat, and protein, as well as hypotension, increased ACTH secretion, impaired fluid excretion, excessive pigmentation, and an inability to tolerate stress. Secondary adrenocortical insufficiency is a far more common problem and results from hypothalamic or administration of exogenous corticosteroids. With the administration of corticosteroids, the feedback system senses the elevated plasma steroid levels and inhibits ACTH production, which, in turn, suppresses adrenal production of cortisol

A common treatment modification of steroid therapy that attempts to minimize adrenal suppression is the alternate-day regimen. This consists of giving steroids in the morning every other day instead of daily, but at a higher dose to maintain an elevated serum level. Because the cortisol level normally is higher in the morning, a single, large dose given at that time has less suppressant effect on ACTH. The time required to regain normal adrenal responsiveness is thought to be 14 day after discontinuing external corticosteroids.

Evidence indicates that the vast majority of patients with adrenal insufficiency may undergo routine dental treatment without the need for supplemental glucocorticoids.

Other than major surgical procedures (e.g., extraction of bony impaction, osteotomy, bone resection, cancer surgery), few dental procedures appear to warrant the use of supplemental steroids before, during, or after the operative period. Patients who are currently taking corticosteroids generally have enough exogenous and endogenous cortisol to handle routine dental procedures, if their usual steroid dose is taken within 2 hours of the surgery. Furthermore, routine dental procedures do not stimulate cortisol production at levels comparable with those that occur at the time of surgery.

At present, for minor oral and periodontal surgery, adrenal insufficiency is prevented when circulating levels of glucocorticoids are about 25 mg of hydrocortisone equivalent per day. This is equivalent to a dose of about 6 mg of prednisone. If the patient is to gain the benefit of the corticosteroid, the drug should be taken within 2 hours of the surgical procedure. Preferably, surgery is scheduled in the morning and stress reduction measures are implemented.

2.The most common form of **hyperadrenalism** is due to glucocorticoid excess (endogenous or exogenous), and it leads to a syndrome known as Cushing's syndrome. This syndrome classically produces weight gain, round or moon-shaped facies a "buffalo hump" on the upper back, abdominal striae and hypertension. Other findings may include glucose intolerance (e.g., diabetes mellitus), heart failure, osteoporosis and bone fractures, impaired healing.

### **21)Pheochromocytoma:**

This is tumor of the adrenal medulla or of the sympathetic paravertebral ganglia. The cardinal symptom is hypertension due to the increased secretion of endogenous epinephrine from these tissues. These patients are also prone to cardiac dysrhythmias. Due to the risk of potentiating cardiovascular problems, the use of vasoconstrictor-containing local anesthetics is contraindicated in these patients. No elective dental treatment should be rendered until the disease is medically corrected. The signs and symptoms of a pheochromocytoma are those of sympathetic nervous system hyperactivity, including: Skin sensations flank pain, elevated heart rate and elevated blood pressure.

### **22)Dental consideration during pregnancy:**

The dentist must keep in perspective the facts of radiation biology. Animal and human data clearly support the conclusion that no increase in gross congenital anomalies or intrauterine growth retardation occurs as a result of exposures during pregnancy totaling less than 5 to 10 centigray (cGy). For comparison, the following may be considered:

Medical chest radiograph results in an estimated fetal or embryonic dose of 0.008 cGy.

A skull radiograph results in 0.004 cGy .

Natural background radiation is approximately 0.0004 cGy daily

A full mouth series of dental radiographs with a lead apron results in 0.00001 cGy

To further reduce the radiation dose, the following measures should be employed: rectangular collimation, E-speed film or faster techniques (digital imaging reduces radiographic exposure by at least 50% compared with E-speed exposures), lead shielding (abdominal and thyroid collar), high kilovoltage (kV) or constant beams, and an ongoing quality assurance program.

The current pregnancy labeling categories are as follows:

A: Controlled studies in humans have failed to demonstrate a risk to the fetus, and the possibility of fetal harm appears remote.

B: Animal studies have not indicated fetal risk, and human studies have not been conducted; or animal studies have shown a risk, but controlled human studies have not.

C Animal studies have shown a risk, but controlled human studies have not been conducted, or studies are not available in humans or animals.

D Positive evidence of human fetal risk exists, but in certain situations, the drug may be used despite its risk.

X Evidence of fetal abnormalities and fetal risk exists based on human experience, and the risk outweighs any possible benefit of use during pregnancy.

Classification of local anesthesia and pain medications:

Drug	FDA Pregnancy Risk Category	Use During Pregnancy	Risk	Use During Breast Feeding
<b>LOCAL ANESTHETICS</b>				
Articaine	C	Use with caution; consult physician		Unknown
Bupivacaine	C	Use with caution; consult physician	Fetal bradycardia	Yes
Etidocaine	B	Yes		Yes
Lidocaine	B	Yes		Yes
Mepivacaine	C	Use with caution; consult physician	Fetal bradycardia	Yes
Prilocaine	B	Yes		Yes
<b>ANALGESICS (NONNARCOTIC)</b>				
Acetaminophen	B	Yes		Yes
Aspirin	C/D <sup>3</sup>	Caution; avoid in third trimester	Postpartum hemorrhage Constriction ductus arteriosus	Avoid
Cyclooxygenase (COX)-2 inhibitor	C	Avoid in third trimester	May lead to constriction, ductus arteriosus	Yes
Diflunisal, etodolac, mefenamic acid	C/D <sup>3</sup>	Use with caution; avoid in third trimester; consult physician	Delayed labor	No
Ibuprofen, flurbiprofen	B/D <sup>3</sup>	Caution; avoid in third trimester	Delayed labor	Yes
Naproxen	B/D <sup>3</sup>	Caution; avoid in third trimester	Delayed labor	Yes
<b>ANALGESICS (NARCOTIC)</b>				
Codeine	C/D*	Use with caution (low dose, short duration); consult physician	Neonatal respiratory depression	Yes
Hydrocodone	C/D <sup>3</sup>	Use with caution (low dose, short duration); consult physician	Neonatal respiratory depression	—
Oxycodone	C/D <sup>3</sup>	Use with caution (low dose, short duration); consult physician	Neonatal respiratory depression	Yes
Pentazocine	C	Use with caution (low dose, short duration); consult physician	Neonatal respiratory depression	Yes
Propoxyphene	C	Use with caution (low dose, short duration); consult physician	Neonatal respiratory depression	Yes

## Classification of antibiotics:

ANTIBIOTICS				
Cephalosporins	B	Yes		Yes
Clindamycin	B	Yes		Yes
Fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, and enoxacin)	C	Use with caution; consult physician	Arthropathy	Caution
<b>Macrolides</b>				
Erythromycin	B	Yes; avoid estolate form		Yes
Azithromycin	B	Yes		Yes
Clarithromycin	C	Use with caution; consult physician		Yes
Metronidazole	B	Yes		Yes
Penicillins	B	Yes		Yes
Tetracycline	D	Avoid	Tooth discoloration, inhibits bone formation	Avoid
Tetracycline (periodontal dosages)	C	Avoid	Tooth discoloration, inhibits bone formation	Avoid

During third semester of pregnancy, the first half is still safe for elective treatments, however these treatments should be avoided in the late third semester. Pt should role on the left side to prevent the supine hypotension. Tylenol is the drug of choice for pain management. NSAID and ASA should be avoided specially in the third semester. Penicillin and clindamycin are safe. In order to prevent hypertensive events, pregnant patient should lay on the left side.

### **23)Endodontic Management in a Patient with Vitamin D-resistant Rickets, Beltes (JOE)**

Vitamin D-resistant rickets (VDRRs) is a rare metabolic disease that occurs in the growing skeleton, having as a cause the X-linked hypophosphatemia. The main cause is mutations in the phosphate-regulating gene with homology to endopeptidase gene, which is expressed in osteoblasts, osteocytes, odontoblasts, and the parathyroid gland, resulting in abnormal osteogenesis and odontogenesis. Patients show normal or low serum calcium, low inorganic phosphate, and high alkaline phosphatase caused by renal phosphate leakage. The prevalence of X-linked hypophosphatemia in North America is 1 in 20,000 persons and is considered the most common form of rickets. In rare cases, VDRRs may occur sporadically, having no other history of the disease in the family.

The disease shows 4 clinical intensities: (1) asymptomatic hypophosphatemia and little or no evidence of metabolic defects mainly found in women, (2) hypophosphatemia with inactive postrachitic deformities in adults, (3) hypophosphatemia and active osteomalacia in adults, and (4) hypophosphatemia with severe systemic bone deformities in young boys. Dental characteristics can be present within a spectrum of manifestations, ranking from mild to severe, based on the number of abscesses as well as radiographic appearance of teeth. Grade I: presents minimum or lack of dental manifestation. Grade II: moderate pulp enlargement with few dental abscesses. Grade III: extremely large pulp chambers and multiple dental abscesses.

## 24)Dentinogenesis imperfecta (DI):

DI represents a group of hereditary conditions that are characterized by abnormal dentin formation. These conditions are genetically and clinically heterogeneous and can affect only the teeth or can be associated with the condition osteogenesis imperfecta. Dentinogenesis imperfecta has been subdivided based on its association with osteogenesis imperfecta (OI) (Type I) or not (Type II) or being associated with the Brandywine triracial isolate and large pulp chambers (Type III). The molecular defects in OI include numerous mutations in the pro-alpha chains of collagen type 1 that result in a phenotype characterized by increased bone fragility

Condition	Clinical Features	Radiographic Features
Osetogenesis Imperfecta with DI (Shields DI type I) <i>(occurs in some forms of osteogenesis imperfecta)</i> (OMIM# <a href="#">166240</a> )	Variable blue-gray to yellow-brown teeth, enamel fracturing, excessive wear, primary teeth usually more affected than permanent	Variable pulp obliteration, bulbous crowns, altered root morphology, increased risk of dentigerous cysts
Dentinogenesis imperfecta (Shields DI type II) (OMIM# <a href="#">125490</a> )	Same appearance and variability as in DI type I. Often similar severity in primary and permanent dentitions	Pulp chamber obliteration that can begin prior to tooth eruption. Abnormal crown and root morphology
Dentinogenesis imperfecta type III (OMIM# <a href="#">125500</a> )	Similar clinical phenotype as DI types I and II although typically severe expression with enamel loss and extensive wear occurring early	Large pulp chambers, Very thin dentin, bulbous crowns and diminished root structure
Dentin Dysplasia type I (OMIM# <a href="#">125400</a> )	Normal clinical crown morphology and coloration in primary and permanent dentitions, Mal-aligned teeth, frequent dental abscess	Pulp obliteration and short blunt roots in both primary and permanent dentitions
Dentin Dysplasia type II (OMIM# <a href="#">125420</a> )	Primary dentition has same phenotype as DI, permanent dentition has normal to slight blue gray discoloration	Pulp obliteration in primary dentition, abnormal pulp morphology and pulp stones in permanent dentition

## 25)Sickle cell (disease) anemia and dental consideration:

Sickle cell hemoglobin (HbS) is the result of substitution of a single amino acid—valine for glutamic acid—at the sixth residue of the chain. In contrast, the thalassemia is another type of hemoglobinopathy, which are caused by deletions or mutations of the gene that result in a defect in globin synthesis (reduced or absent synthesis of one or more globin chains).

The two most common types are **sickle cell trait** and **sickle cell (disease) anemia**. **Sickle cell trait** is the heterozygous state in which the affected individual carries one gene for HbS. **Sickle cell anemia** is the homozygous state.

The RBC in sickle cell anemia becomes sickle shaped when blood experiences lowered oxygen tension or decreased pH, or when the patient becomes dehydrated. This results in partial crystallization of HbS, polymerization, and realignment of the defective Hb molecule. Clinical signs and symptoms of sickle cell anemia are the result of chronic anemia and small blood vessel occlusion.

Screening tests should include complete and differential blood counts, a smear for cell morphologic study, Hb or hematocrit count, a Sickledex test (for African Americans), and platelet count. For minimal medical complications, the patient's Hb should be above 11 g/dL and the patient should be free from symptoms. Patients who are short of breath and who have Hb < 11 g/dL, an abnormal heart rate, or an oxygen saturation less than 91% (as determined by pulse oximetry) are considered unstable, and routine treatment should be deferred until their health status improves.

African Americans with sickle cell anemia can receive routine dental care during noncrisis periods; however, long and complicated procedures should be avoided. Good dental repair and preventive dental care are important because oral infection can precipitate a crisis. If infection occurs, it must be treated expeditiously through local and systemic measures such as incision and drainage, heat, high doses of appropriate antibiotics, pulpectomy, and/or extraction. Prophylactic antibiotics are recommended for sickle cell anemia when major surgical procedures are performed to prevent wound infection or osteomyelitis. Penicillin is the drug of choice in nonallergic patients. Intramuscular or IV antibiotics should be considered for use in sickle cell anemic patients who have an acute dental infection.

#### Dental Management of the Patient With Sickle Cell Anemia

1. Confirm with patient's physician that the condition is stable.
2. Arrange short appointments.
3. Avoid long and complicated procedures.
4. Maintain good dental repair.
5. Institute aggressive preventive dental care.
  - a. Oral hygiene instruction
  - b. Diet control
  - c. Toothbrushing and flossing
  - d. Fluoride gel application
6. Avoid oral infection; treat aggressively when present.
7. Use pulse oximeter, maintain O<sub>2</sub> saturation above 95%.
8. Use local anesthetic without epinephrine for routine dental care. For surgical procedures, use 1:100,000 epinephrine in local anesthetic.
9. Avoid barbiturates and strong narcotics; sedation may be attained with diazepam (Valium).
10. Use prophylactic antibiotics for major surgical procedures.
11. Avoid liberal use of salicylates; control pain with acetaminophen and codeine.
12. Use nitrous oxide-oxygen with greater than 50% oxygen, high flow rate, and good ventilation.

## 27)Thyroid Diseases:

Generalized enlargement of the thyroid gland, referred to as a *goiter*. The goiter of Graves' disease is associated with hyperthyroidism. Hashimoto's thyroiditis leads to hypothyroidism and thyroid enlargement.

The thyroid gland secretes three hormones: thyroxine ( $T_4$ ), triiodothyronine ( $T_3$ ), and calcitonin. Thyroid hormone influences the growth and maturation of tissues, cell respiration, and total energy expenditure. Calcitonin is involved, along with parathyroid hormone and vitamin D, in regulating serum calcium and phosphorous levels and skeletal remodeling. Blood levels of  $T_4$  and  $T_3$  are controlled through a feedback mechanism mediated by the hypothalamic- pituitary-thyroid axis.

\*The term *thyrotoxicosis* refers to an excess of  $T_4$  and  $T_3$  in the bloodstream. The most common symptoms are nervousness, fatigue, rapid heartbeat or palpitations, heat intolerance, and weight loss. Palmar erythema may be present, profuse sweating is common, and excessive melanin pigmentation of the skin occurs in many patients; however, pigmentation of the oral mucosa has not been reported.  $T_4$ ,  $T_3$ , TBG, and TSH tests can be used to screen for hyperthyroidism. However, current practice is to screen patients suspected of being hyper- thyroid with use of the TSH serum level and to measure or estimate the free  $T_4$  concentration.

\*Hashimoto's thyroiditis is the most common cause of primary hypothyroidism in the United States. It is an autoimmune disorder that presents most often as an asymptomatic diffuse goiter. High titers of circulating thyroid autoantibodies and thyroid antigen-specific T cells are observed. It usually affects young and middle- aged women. Goiter is the hallmark of Hashimoto's thyroiditis. Over time, most patients develop hypothyroidism as lymphocytes replace functioning tissue. In a few cases, the patient develops transient hyperthyroidism, to be followed later by hypothyroidism

The use of epinephrine or other pressor amines (in local anesthetics or gingival retraction cords, or to control bleeding) must be avoided in the untreated or poorly treated thyrotoxic patient. However, the well-managed or euthyroid thyrotoxic patient presents no problem in this regard and may be given normal concentrations of these vasoconstrictors. Also, once the hypothyroid patient is under good medical care, no special problems in terms of dental management remain, except for the need to address malocclusion and enlarged tongue, if they are present.

## 28) Most common emergencies in dental office:

Over 60% of the emergencies were syncope, with hyperventilation the next most frequent at 7%. In the United States and Canada, studies have also shown that syncope is the most common medical emergency seen by dentists.

**Syncope:** The most common type of syncope is peripheral vascular (circulatory or vasovagal) syncope.

Regardless of the trigger, the mechanism of syncope is similar in the various vasovagal syncope syndromes. Syncope happens as a result of simultaneous enhancement of parasympathetic nervous system (vagal) tone and withdrawal of sympathetic nervous system tone.

This results in a spectrum of hemodynamic responses:

1. On one end of the spectrum is the **cardioinhibitory** response, characterized by a drop-in heart rate (negative chronotropic effect) and in contractility (negative inotropic effect) leading to a decrease in cardiac output that is significant enough to result in a loss of consciousness. It is thought that this response results primarily from enhancement in parasympathetic tone.
2. On the other end of the spectrum is the **vasodepressor** response, caused by a drop-in blood pressure (to as low as 80/20) without much change in heart rate. This phenomenon occurs due to vasodilation, probably as a result of withdrawal of sympathetic nervous system tone.

## Hyperventilation:

Excessive rate and depth of respiration leading to abnormal loss of carbon dioxide from the blood primarily predisposed to anxiety. Hyperventilation symptoms usually happen in younger people. Hyperventilation is characterized by rapid short strained breaths, cold Sweats, palpitation, chest muscle fatigue. Prevention includes practicing stress reduction protocols.

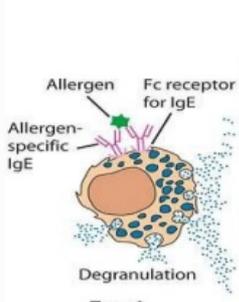
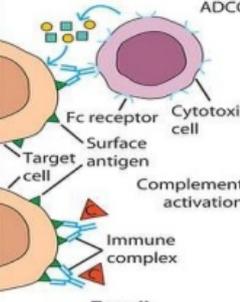
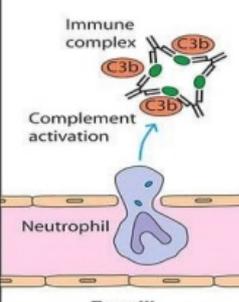
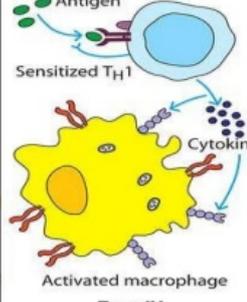
As anxiety increases, rate and depth of respiration Increase. This lead to O<sub>2</sub>/CO<sub>2</sub> exchange by lungs. Excessive CO<sub>2</sub> blow off that decrease the paCO<sub>2</sub> (Hypocapnia). This will lead to an increase in blood pH (RESPIRATORY ALKALOSIS). When hyperventilation leads to respiratory alkalosis, it may cause a number of physical symptoms: dizziness, tingling in the lips, hands or feet, headache, weakness, fainting and seizures. In extreme cases, it can cause carpopedal spasms (flapping and contraction of the hands and feet). For treatment instruct the patient to be calm and breathe slowly and have patient breathe slowly into a paper bag.

## 29) Hypersensitivity:

Natural rubber latex is known to cause Type I and Type IV allergic reactions, as well as irritant contact dermatitis. Type I The most serious and rare form of latex allergy, Type I hypersensitivity can cause an immediate and potentially life-threatening reaction, not unlike the severe reaction some people have to bee stings. Such reactions account for a significant proportion of perioperative anaphylactic reaction, especially in children with myelomeningocele. Type I natural rubber latex allergy is an IgE (immune) mediated reaction to proteins found in the *Hevea brasiliensis* tree, a type of rubber tree. Testing for type I natural rubber latex allergy is through blood testing to determine if the patient is producing IgE antibodies to latex proteins. Anaphylactic shock can be provoked in allergic persons by the previous use of latex in an area.

Type IV allergy, also known as allergic contact dermatitis. It can be diagnosed through a positive skin patch test, although a negative test does not rule out a latex allergy. This reaction is mediated by APC, THP-1 cells and INF, TNF-beta and IL-2 cytokines.

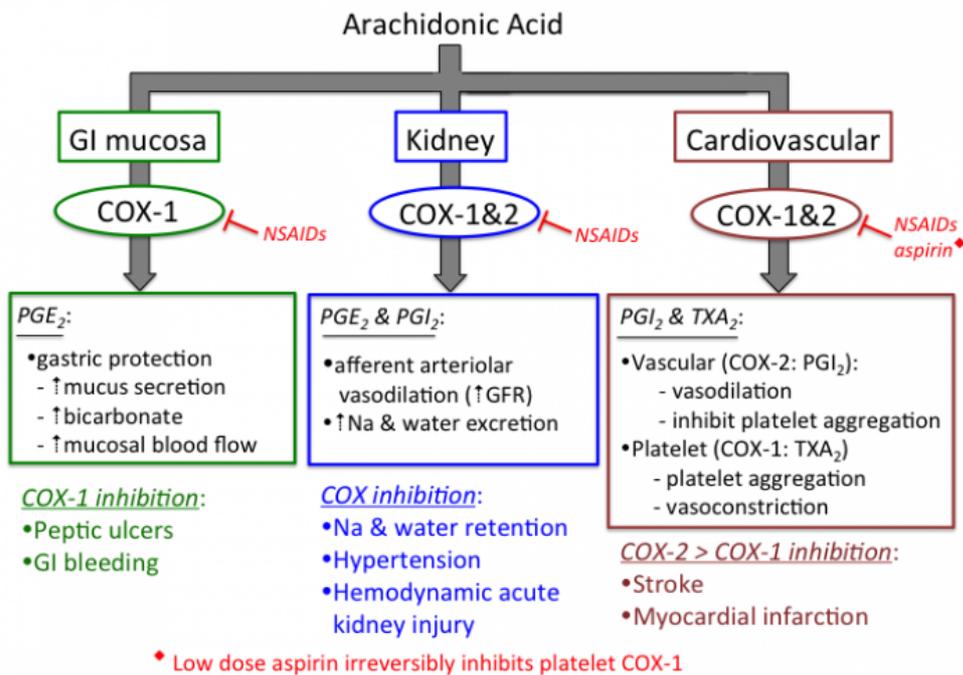
## Hypersensitivity Reactions

 <p><b>Type I</b></p>	 <p><b>Type II</b></p>	 <p><b>Type III</b></p>	 <p><b>Type IV</b></p>
<p>IgE-Mediated Hypersensitivity</p>	<p>IgG-Mediated Cytotoxic Hypersensitivity</p>	<p>Immune Complex-Mediated Hypersensitivity</p>	<p>Cell-Mediated Hypersensitivity</p>
<p>Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators</p>	<p>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC</p>	<p>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils</p>	<p>Sensitized <math>T_H1</math> cells release cytokines that activate macrophages or <math>T_C</math> cells which mediate direct cellular damage</p>
<p>Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema</p>	<p>Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia</p>	<p>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus</p>	<p>Typical manifestations include contact dermatitis, tubercular lesions and graft rejection</p>

## Drug interaction in dentistry

NSAIDS mechanism of action:

### NSAID Side Effects:



COX-1 is constitutively expressed and produces PGs that are involved in basic housekeeping functions such as cytoprotection in the stomach, regulation of blood flow in the kidneys, and the formation of thromboxane A<sub>2</sub>. The formation of thromboxane A<sub>2</sub> can ultimately lead to platelet aggregation; therefore, inhibition of thromboxane A<sub>2</sub> should decrease platelet aggregation. COX-2 is inducible, synthesized in inflamed tissues (including dental pulp), and is important in the production of the proinflammatory PGs as well as the vasodilating prostacyclin (PGI<sub>2</sub>). Although they do not produce pain if applied alone, PGs are known to sensitize peripheral nociceptors, which increases the algogenic (pain-producing) properties of serotonin and bradykinin.

Anti-inflammatory drugs, corticosteroids, or immunomodulators, which can have an impact on dental care. The use of anti-inflammatory drugs and the involvement of the intestinal tract suggest that aspirin and other NSAIDs are to be avoided in patients with ulcerative colitis. Acetaminophen may be used alone or in combination with opioids. Alternatively, co-therapy with a COX-2 inhibitor (celecoxib) and a PPI can provide pain relief and simultaneous protection of the gastrointestinal mucosa.

## Common pain medication drug interactions:

Dental Drug	Interacting Drug	Medical Condition/Situation	Effect
Aspirin	Diltiazem	Hypertension, angina	Enhanced antiplatelet activity of aspirin. <b>RECOMMENDATION: Monitor for risk of prolonged bleeding with the use of PFA-100.</b>
NSAIDs	Beta blockers, ACE inhibitors	Hypertension, post myocardial infarction	Decreased antihypertensive effect. <b>RECOMMENDATION: Limit duration of NSAID dosage to about 4 days.</b>
NSAIDs	Lithium	Manic depression	Produces symptoms of lithium toxicity, including nausea, vomiting, slurred speech, and mental confusion. <b>RECOMMENDATION: NSAIDs should not be prescribed to patients who take lithium. It can result in toxic levels of lithium, or consult with physician to reduce lithium dose.</b>
NSAIDs (Naproxen)	Alendronate	Osteoporosis, multiple myeloma	Increased risk for gastric ulcers. <b>RECOMMENDATION: Use acetaminophen products.</b>
NSAIDs	Methotrexate (MTX)	Connective tissue disease, cancer therapy	Toxic level of methotrexate may accumulate. <b>RECOMMENDATION: Avoid interaction if on high-dose MTX for cancer therapy. Low-dose MTX for arthritis is not a concern.</b>

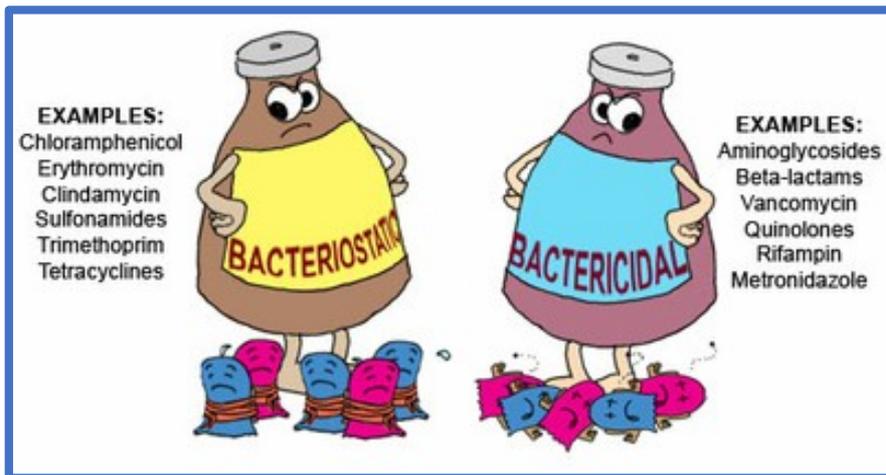
Common drugs prescribed by dentists, risk of drug–drug interactions, and potential management options (BDJ, Dawoud, 2014):

Drugs prescribed by GDP	Interacting drug	Risk of interaction	Potential management options
Adrenaline-containing local anaesthetics	Beta-blockers	Hypertensive response possible	Limit dosage of LA to 3–4 cartridges or use adrenaline-free LA
	Tri-cyclic antidepressants	Increased sympathomimetic response	Limit dosage of LA to 3 cartridges or use adrenaline-free LA
	General anaesthetic agents (eg propofol)	Potentiates hypertensive drugs leading to dangerous hypotension	An anaesthetist manages these patients carefully
Non-steroidal anti-inflammatories (NSAIDs)	Anticoagulants (warfarin, coumarins)	Increased risk of bleeding	Careful use of NSAIDs or consult doctor
	ACE inhibitors, beta-blockers, diuretics	NSAIDs decrease hypotensive effect of drugs	Careful use of NSAIDs or consult doctor
	Aspirin	Increased risk of bleeding	Avoid use of aspirin or consult doctor
	Methotrexate	Increased methotrexate toxicity	Consult doctor before advising patients
Macrolide antibiotics (erythromycin, clindamycin)	SSRIs	Increased risk of bleeding	Careful advice of use of NSAID
	Calcium channel blockers (CCBs)	Increased and prolonged hypotensive effect of CCBs	Avoid use of macrolides and use alternative antibiotic
	Simvastatin	Increased chance of muscle toxicity	Avoid use of macrolides
Metronidazole	Clopidogrel	Increased risk of bleeding	Avoid use of macrolides
	Warfarin	Increased risk of bleeding	Avoid use of macrolides
	Warfarin	Increased risk of bleeding	Avoid use of metronidazole
	NSAIDs	Increased risk of bleeding	Avoid use of NSAIDs
Azole antifungals	Phenytoin	Effect of phenytoin may be increased	Monitor patient closely or prescribe alternative antibiotic
	Warfarin	Increased risk of bleeding	Avoid use of azoles – prescribe nystatin instead
Penicillin-based antibiotics	Simvastatin	Risk of muscle toxicity	Avoid use and prescribe alternative antifungal
	Oral contraceptive pill	Decreased contraceptive effect	Advise use of barrier contraceptives
	Warfarin	May increase risk of bleeding	Patients should be advised to be vigilant for any signs of increased bleeding, if in doubt consult doctor
	Methotrexate	Increased risk of methotrexate toxicity	Risk with high dose penicillins, give lower dosage and monitor closely

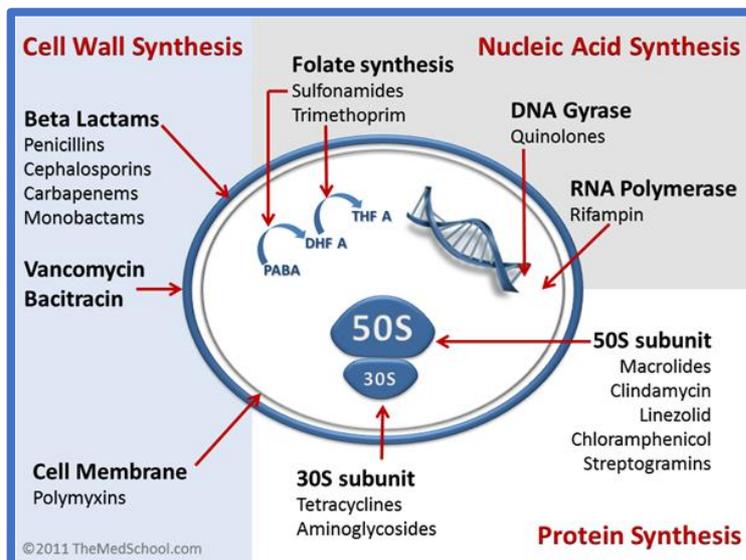
Key: ACE: angiotensin-converting enzyme; CCB: calcium channel blocker; LA: local anaesthetic; NSAID: non-steroidal anti-inflammatory drug; SSRI: selective 5-hydroxytryptamine reuptake inhibitor

Lithium is used as a first line maintenance therapy for bipolar disorder and as a mood stabilizer. Nephrotoxic medications such as COX-2 inhibitors and NSAID can affect the pharmacokinetics and metabolizing of lithium and can lead to serious adverse effects.

**Classification of antibiotic based on Cidal- Static:**



**Antibiotic mechanism of action:**



## Possible drug interactions following administration of antibiotic and antifungal:

DENTAL DRUG	INTERACTING DRUG	RESULT/MANAGEMENT
Ampicillin	Atenolol (Tenormin, g)	Atenolol bioavailability may be reduced.
Cephalosporin	Anticoagulants (Coumadin, g)	Risk of bleeding disorders might be increased in anticoagulated patients.
Clindamycin	Erythromycin	Possibility of antagonism. AVOID CONCURRENT USE.
Macrolides clarithromycin erythromycin	Anticoagulants (Coumadin, g)	Risk of bleeding disorders is increased in anticoagulated patients. Monitor pt.
	Benzodiazepines	Increased benzodiazepine levels resulting in CNS depression. Avoid combination in elderly.
	Cyclosporine	Increased cyclosporine renal toxicity. Consult MD.
	Digoxin	Increased digoxin levels in 10% of patients. May use cautiously.
	Statins	Increased statin levels with possible muscle toxicity. AVOID CONCURRENT USE
Metronidazole	Anticoagulants (Coumadin)	Risk of bleeding disorders is increased in anticoagulated patients. Consult MD.
	Barbiturates	Decreased metro. Levels. Increase dose.
	Lithium	Increased lithium levels with possible toxicity. Consult MD.
Systemic Azole Agents (fluconazole, itraconazole, ketoconazole)	Anticoagulants (Coumadin)	Risk of bleeding disorders is increased in anticoagulated patients. Consult MD.
	Rifampin	Decreased levels of the antifungal
	Digoxin	Increased digoxin levels. AVOID COMBINATION.

### **Interaction between antibiotics and oral contraceptive:**

Antibiotics can interrupt the enterohepatic cycling of estrogens by reducing the bacterial population of the small intestine, which is responsible for hydrolysis of the glucuronide moiety (estrogen metabolite found in bile) to free drug. When the gut flora is altered, enterohepatic circulation is reduced, the metabolite is excreted, resulting in lower circulating concentrations of ethinylestradiol. Many antibiotics are believed to decrease oral contraceptive efficacy in this manner, including penicillins, cephalosporins, tetracyclines, macrolides, antifungals, metronidazole, sulphonamides and antituberculosis agents. However, Rifampin is the only antibiotic to date that has been reported to reduce plasma estrogen concentrations. Oral contraceptives cannot be relied upon for birth control while taking rifampin. It is okay to use dental antibiotics. Provide advice to patient as to the potential risk and for consideration of additional contraceptive measures.

### **HMG-CoA reductase inhibitors (-Statins):**

The cytochrome P450 (CYP) enzyme system plays an important part in the metabolism of the statins, leading to clinically relevant interactions with other agents, particularly cyclosporin, erythromycin, itraconazole, ketoconazole and HIV protease inhibitors, that are also metabolized by this enzyme system. In clinical practice, the risk of a serious interaction causing myopathy is enhanced when statin metabolism is markedly inhibited. Thus, rhabdomyolysis has occurred following the co-administration of cyclosporin, a potent CYP3A4 and P-glycoprotein inhibitor, and lovastatin

### **Anti-viral therapy in HIV:**

AZT (Zidovudine) A nucleoside reverse transcriptase inhibitor that interferes with viral RNA-dependent DNA polymerase, an enzyme necessary for viral HIV replication.

Therapeutic Effect: Interferes with HIV replication, slowing the progression of HIV infection. AZT should be used with cautions with acetaminophen and clarithromycin due to decreased plasma levels of the drug.