Principles of Drug Therapy in Dentistry

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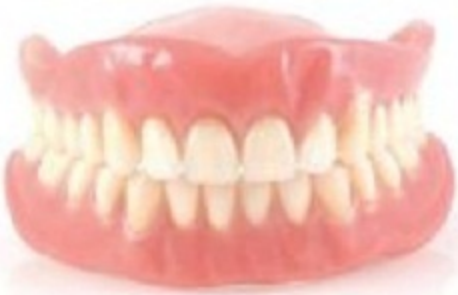
Foreword
Sanna Shafshak



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Dedicated to

My Father
My Mother
My Wife
and My sons Sajjad and Ali

Foreword

This book is a model for merging two intimately integrated sciences—oral diagnosis and pharmacology. It is a very helpful guide to dental practitioners since it relates diagnostic criteria of oral diseases to detailed medical treatment.

The author is also an excellent model for graduates of Misr University for Science and Technology (MUST), 6th of October City, Giza, Egypt.

Dr Hussain proved the accuracy of the vision of the university as it was first stated by Prof (Dr) Soad Kafafy, the founder of the university.

"The vision that aims at graduating dentists with higher capabilities than just practice dentistry."

Hussain has to be appreciated for the great efforts he made and for his will and courage to make this book.

Sanna Shafshak
Professor of Oral Diagnosis
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Preface

It is not an easy task to cover all drugs used in dentistry; but in this book, the author summarized the most fundamental items.

The mouth and oral cavity is considered as the body gates for either good health or diseases.

Oral hygiene and good health are the first line of prophylactic treatment in dentistry.

The curative medicines and drugs used in management of oral diseases are mentioned in chapters, to facilitate understanding and help both undergraduate and postgraduate people who are concerned with dentistry.

- Gives an introduction to general pharmacology and general forms and routes of administration of the drugs routinely used. It also outlines the basics of drug interactions.
- The **first chapter** discusses all types of dental pain and their characters, pathogenesis of inflammation and its body response and influence.
- The **second chapter** is concerned with all antimicrobial agents treating bacterial diseases either prophylactic or curative, and specific or nonspecific.
- The **third** and **fourth chapters** deal with antifungal and antiviral agents in common use, putting in consideration—the indications, contraindications, side effects and drug interactions for each drug.
- The **fifth chapter** is the most important one, because an emergency is a life-threatening condition. Dentists should know very well how to deal, manage and take prompt action in such a way to save patient's life. All physicians, pharmacists, and before all dentists should keep that chapter as a booklet for emergency cases.

The author has done his best to present this book in such informative and comprehensive manner.

Members of Pharmacology Department, Faculty of Pharmacy, MUST, have shared in revising and summarizing the main topics to be easily digested by the readers.

We were keen to minimize and maximize the items according to its medicinal and surgical significance for dentists.

Hussain Ali

Acknowledgments

I wish to express my thanks and appreciation to everybody interested in supporting and helping me. In the first place, all thanks go to "Allah" who provided us with knowledge and the ability to gain it.

I am more than grateful to my wife "Maryam" for standing with me in the hard times.

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A special recognition goes to Dr Husseiny Elgendy, Professor of Pharmacognosy, as he was interested in revising the book. His notes were more than important as well as his suggestions. He did motivate and encourage me.

Dr Salah Lofty, Assistant Lecturer and the right hand of Dr Elgendy, was more than a valuable source of help and support. He actively revised the book and provided me with valuable references.

My colleagues and friends, who deserve special recognitions and thanks include, Ahmad Al Maskeen and the "Two Alis"—Ali Al Hassar and Ali Sulais, for their support and provision of computer assistance. Thanks also go to Thani Al Sharrari and to the "Two Hussains"—Hussain Shakhory and Hussain Saeed, for their continuous support and motivation. Thani was more than interested in helping and providing me with ideas and resources.

Contents

Chapter 1

Introduction

For most people, the first impression about a doctor is someone who writes a drug prescription. In dentistry, however, a dentist is usually concerned about removal of the cause rather than instructing patients to use certain drugs, possibly as the cause is accessible for removal and that drugs alone are not sufficient to produce total therapeutic effects. However, a dentist should complement the provided dental treatment with a proper drug for the comfort and, sometimes, the safety of the patient. In order to administer a drug safely, the dentist should have sufficient knowledge about its mechanism of action, indications, contraindications, adverse reactions and interactions with other drugs. The risks of drug therapy to medically complex patients increase as these patients have weaker homeostatic systems. When in doubt, it is always better to seek advice from a specialist. Table 1.1 shows some important definitions regarding use and handling of drugs.

Table 1.1: Some important definitions

Drug	A substance used or intended to be used for therapeutic reasons (diagnosis, prevention or treatment).
Pharmacology	The science which is concerned about drugs, including their source, properties, uses, contraindications and adverse reactions. Its main branches include: Pharmacokinetics, pharmacodynamics and pharmacotherapeutics.
Pharmacokinetics	Branch of pharmacology, concerned about what the body does to the drug like absorption, distribution, metabolism and excretion.
Pharmacodynamics	The branch which deals with the biochemical effects (mechanism of action) of the drug on the body or microorganisms.
Bioavailability	It is the percentage of the administered drug which reaches the blood circulation in unchanged state.
Drug metabolism	It is the process by which the drug is inactivated, broken down and excreted. By the action of specific enzymes, the lipophilic drug is converted into hydrophilic one.
Adverse drug reactions (ADRs)	Harmful or at least unwanted effects produced by normal dose of a drug. ADR differs from side effects as the latter can be useful.
Drug interaction	Alteration in the expected effects of a drug when administered with another one or with food/drinks.
Antidote	A substance which is used to counteract the effects of toxic agent or poisoning.

ROUTES OF DRUG ADMINISTRATION AND DRUG FORMS

The route of drug administration depends primarily on the therapeutic requirement, that is, whether the needed effects are local or systemic, in addition to the required speed of onset, duration and concentration of the drug (Table 1.2). Sometimes, the drug properties (irritation, solubility, instability) make it impossible to be used by all routes.

Enteral (Oral) Route

This is the simplest and most common route of drug administration. The patient is able to self-medicate himself and the overall procedure requires only a cup of water. Absorption of a drug via this route is achieved by the GIT mucous membrane being most active in the small intestine (duodenum). The small intestine provides the largest surface area through the presence of villi and microvilli, wider pH range for drug stability and higher membrane permeability. Other parts like the stomach and large intestine also exhibit absorption but of less significance. The stomach is a harsh environment for a drug because of its low pH. Furthermore, the stomach is lined by a thick mucus layer which embeds drug absorption.

Table 1.2: Routes of drug administration

Enteral
- Oral
- Buccal (sublingual)

Parenteral
- Intradermal
- Subcutaneous
- Intramuscular
- Intravascular
- Inhalational

Local delivery
- Topical

The bioavailability of an oral drug may be affected by several factors, like gastric acidity, presence of food, gastric emptying, digestive and cytochrome enzymes and hepatic first pass metabolism. In addition, the onset of the drug is slow. Possible gastric irritation and inability to be used in unconscious or uncooperative patients are further disadvantages. This makes oral form unsuitable for emergencies or life-threatening situations.

Sublingual or Buccal Route

It utilizes the richly supplied thin mucous membrane of the mouth for rapid absorption. Although retained in the mouth, the intended effects of the drug are systemic. The absorbed agent escapes the hepatic metabolism as it is driven directly to the target cells via the superior vena cava. Therefore, the sublingual route provides higher bioavailability than the oral one, in addition to its possible use in unconscious or vomiting patients. Nitroglycerin, a vasodilator used in case of angina pectoris, exhibits more than 90 percent metabolism by the hepatic system. For that reason, nitroglycerin is used sublingually. The drug forms that can be present for oral routes are listed in Table 1.3.

Parenteral Route

By this route, the drug is brought directly into blood or tissue fluids. This route helps in administering those agents unstable in or those poorly absorbed from the GIT environment. The bioavailability is higher than the oral route and the onset of action is more rapid. This facilitates the management of unconscious patient or in case where prompt action is needed. One main disadvantage is that once administered by parenteral route, the drug effects cannot be reversed. Other inconveniences include painful procedure, the need for professional administration and practice of asepsis.

Intravascular or Intravenous (IV) Routes

They bring the drug into arterial or venous blood, respectively. These routes provide 100 percent bioavailability and most rapid onset of action. These also provide the best control over the amount

Table 1.3: Drug forms used by the oral route

Tablets	Solid dosage form orally placed and swallowed. When placed in water, tablets disintegrate.
Enteric coated (EC) tablet	A layer of cellulose acetate coating is used to protect the active agent form gastric acidity and prevent gastric irritation.
Sugar coated tablet	Sugar layer used to produce palatable tablets.
Film coated tablet	This layer enhances swallowing, stabilizes the agent against moisture and improves taste.
ODT*	Tablets laid on the tongue and left to disintegrate. Useful for those who cannot swallow.
Capsules	Gelatin shell (hard or soft) used to protect the drug against temperature, humidity and to enhance swallowing.
Caplets	Tablets in the form of capsule and with the texture of gelatin (tablets easy to swallow as capsules).
Solutions	Homogeneous liquid form by solute (active agent) dissolved in solvent.
Suspension	Heterogeneous liquid with fine particles of solute distributed uniformly. The formula settles down with time and gets redispersed when shaken.
Emulsion	Liquid with two different phases, like water and oil with an emulsifying agent.

* ODT: Orally Disintegrating Tablet

of active agent provided. However, it may result in most severe adverse reactions in addition to possible hemolysis and thrombophlebitis. The used solutions are only aqueous and no depot (nonaqueous medium) or suspensions are to be used by this route. The injection can be in the form of bolus (initial large dose), slow injection (over 15–20 minutes) or slow infusion (large volume of drug over long period of time).

Intramuscular (IM) Injection

It provides rapid action, but not as the IV route. Large muscles like the deltoid, gluteus or the triceps are the target for IM injections. Muscles have good blood supply, which helps in providing uniform absorption. However, IM injections are quite painful especially with depot solutions.

Subcutaneous (SC) Injections

These utilize the blood circulation in the connective tissue underneath the skin. Vascularity in this area is quite low and this produces uniform and prolonged duration of action but with slow onset. The duration of action can be further prolonged by the addition of vasoconstrictors. Hyaluronidase enzyme, on the other hand, enhances absorption by the SC route.

Inhalational Route

Its uses drugs in the gaseous state. Volatile liquids or aerosols can also be used. Absorption in this route is achieved via the mucous membrane of the respiratory tract and/or the pulmonary epithelium. The advantage of this route is that rapid action can be achieved as large surface area is utilized along with rich blood supply. In addition, local effects can be produced if the target is the respiratory system.

Topical Delivery of Drugs

The main aim of topical application of drugs is to provide high drug concentration at the desired site.

Because this route of drug therapy acts only on superficial tissues, minimal systemic involvement and minimal systemic adverse reactions are expected. The procedure of applying a topical agent is noninvasive and provides psychological relieve as patients can take care of themselves. However, the contact time between the drug and the target tissues is short due to wiping or washing effects. In addition, the surface area can be small, especially periodontal pockets. This would necessitate the use of a device which slowly releases the active ingredients. Forms of topical agents are listed in Table 1.4.

WRITING PRESCRIPTIONS

A prescription is a way of communication between a physician or a dentist and the pharmacist. This can be in the written or verbal forms. The prescription is considered as a part of the medicolegal documents and both the prescriber and the pharmacist are in charge. It should be written neatly, with full and clear information regarding the type, dose and duration of the drug therapy. Care should be practiced also when using symbols and abbreviations as they may increase the chance of confusion.

When a drug is prescribed, the nonproprietary or the common name should be used first. This name is the primary ID of the drug and each drug has only one nonproprietary name but many proprietary ones. For example, paracetamol is the nonproprietary name for the commonly known analgesic, while proprietary names as *panadol*, *adol*, and many others exist. In this book, the

Table 1.4: Drug forms used by the topical route

Lozenges	Large tablets held in the mouth to dissolve and produce local action. The active agent is placed in sugar base.
Pastilles	Similar to lozenges, but with jelly like consistency.
Ointment	Semisolid preparation for external use. It usually has hydrating effects and used on dry skin.
Cream	Similar to ointment, but without the hydrating effect.
Paste	Semisolid agent but with solid particles at greater concentration when compared to ointment, which produces stiffer or more viscous preparation.
Gel	Translucent, non-greasy semisolid with higher water or alcohol percent than creams or ointment. Gelling agent is used to produce the semisolid consistency.
Solution	Liquid preparation with the active agent dissolved in a solvent. The formula is low in viscosity and allows its use as a mouthwash or gargle.
Paint	Active agent is placed in a volatile medium (for skin use) or in viscous one (for use in mucous membrane).

nonproprietary names are used mainly with some common proprietary ones written in *bold blue* underneath.

A prescription is designed to contain the basic information about the patient, the prescriber and the drug. The patient's name, age and sex should be provided to confirm the drug dosage by the pharmacist. The name and telephone number of the prescriber should be also provided for reference. All this information is contained in what is called the superscription. In addition, the superscription also contains the symbol R_x, which stands for "recipe" (Table 1.5 for more abbreviations). The next part of the prescription is its body or what is called the inscription. This part contains the information about the prescribed drug. It is written below and right to the symbol R_x. It starts by the name of the drug (the nonproprietary followed by the proprietary if to be written). The dosage, frequency and amount are written next. The subscription, which is written below the inscription, usually contains instructions to the pharmacist about the form of the drug or the quantity. This

Table 1.5: Some abbreviations used in prescription writing

English	Latin	Abbreviations
Recipe		R_x
By mouth	Per os	po
Once per day	Onus in die	od
Twice per day	Bis in die	bid
Three times a day	Ter in die	tid
	Ter in die sumendum	tds
Four times a day	Quarter in die	qid
Every hour	Quaque hora	qh
As needed	Si opus sit	sos
Before meal	Ante cibum	ac
After meal	Post cibum	pc
Tablet	Tabella	Tab
Capsule	Capsula	Cap

is especially important in case of, the prescribed drug is a controlled one. When the prescriber wishes the written instructions to be provided on the containers of the drugs, the word "label" or "signa" is written. Some prescription forms contain the word label with a table before it to be ticked. This part containing the instruction to be provided to the patient is known as the transcription. Better patient compliance is expected when the drug is labeled as patients usually forget verbal instructions. The last part would be the signature of the prescriber, which is mandatory in case of controlled drugs. The name of the prescriber is handwritten followed by the professional degree. The name can be stamped one line under the signature. Table 1.6 shows an example, of a blank prescription.

GENERAL CONSIDERATIONS

For best results, the patient's compliance should be optimized. The choice of the drug, its form and route of administration should be suitable to the patient. For more convenience, the oral form is the

Table 1.6: Sample of a prescription form

Superscription :	Dr Name_____
	Telephone _____
	Address _____
	Patient's name _____
	Age ____ Sex _____
	Address _____
	R_x
Inscription	
Subscription	Refill
	0 1 2 3
Transcription or signa	■ Label
Signature _____	

most commonly chosen one. For children or those unable to swallow tablets, the liquid form is the right choice. However, the parenteral route may be indicated when the condition is serious. In emergencies, drugs are usually provided in the injection form. SC injections should be avoided in shocked patients as the blood circulation is poor in the subcutaneous tissue.

The timing of the drug intake can further affect the patient's compliance. Whenever possible, a drug which needs lower frequency of intake should be chosen, for example, every 12 hours instead of every 6 hours. In case of multidrug therapy, combination should be made as possible to lessen the number of taken drugs.

Good communication with the patient should be established and the drug benefits and its method of use should be explained. The instructions of use should be provided both in verbal and written forms. The patient should be informed of possible adverse reactions and if any precautions to be undertaken.

SPECIFIC CONSIDERATIONS

The doses and frequencies of intake presented in this book are for average adults (18 years and above) weighing about 70 kg. The dose, however, is affected by the patient's age, weight and medical condition. Children, underweights, elderly and medically complex patients need dose modification in order to provide a drug without possible toxicity.

For children, the dose is adjusted following Clark's or Young's rule (Table 1.7). Clark's rule, however, provides more accurate results.

Table 1.7: Dose adjustment for children

Clark's rule
Child dose = Child's weight/150 × adult dose
Young's rule
Child dose = Age/age + 12 × adult dose*

* This means that a 12-year-old child can use half adult dose

In case of renal or liver disease, the ability of the body to breakdown and eliminate the drug is reduced and, accordingly, either the dose or the frequency of drug intake should be reduced. Whenever possible, medical consultation should be made.

Pregnancy and breastfeeding are two physiological conditions that may require the clinician to avoid those agents with possible teratogenic or adverse effects on the developing fetus or the breastfeeding infant. A section of those special patients is present at the end of each chapter denoting these agents that should be avoided and those that can be used safely.

The basics of drug interaction are presented at the drug interaction (Box 1.1). At the end of each chapter, a box containing the possible drug interactions is also presented.

Box 1.1: Drug interaction (Basic concepts)

Drug interaction is the process by which the expected effects of a drug is altered by the use of another drug, food, drink or environmental chemical agent. The incidence of drug interaction is expected to be higher in those under multidrug therapy, elderly or those with severe chronic diseases (renal or hepatic for example). The altered drug effect can be increased, decreased or totally not related to the parent drugs. The following terms should be defined:

Antagonism is the process by which the effects of a drug is decreased or blocked by the action of another. It may be produced by the following mechanisms:

- When two effects are produced but not for the benefit of each other; for example, the use of tetracycline decreases the effects of penicillin, as the former decreases protein synthesis while the later acts by inhibiting cell wall synthesis
- When two agents compete for the same receptor. Naloxone and flumazenil would terminate the effects of opoids and benzodiazepine, respectively
- When two drugs with opposite actions are given concurrently. An example would be the administration of insulin and corticosteroids

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- When the administered agents have direct physical or chemical effects on each other. For example, the use of antacids with tetracycline would produce nonabsorbable complexes
- When one drug affects the metabolism of another either by affecting its metabolizing enzymes or its rate of excretion.

Potentiation is the process of increasing the action of one drug by another drug which is therapeutically unrelated to the former. Probenecid (uricosuric agent used to decrease uric acid) increases the effects of penicillin as it decreases in tubular excretion.

Unexpected effects are associated with the production of highly active metabolite by the interaction of two drugs. This effect is not experienced when any of them is used. An example would by the use of metronidazole with alcohol, which increases the level of acetaldehyde.

Summation interaction is produced when the use of two related agents produces the combined actions of both. An example, would be the use of opoids and general anesthetics.

Synergism is the increased quantitative effects of one of two concurrently given drugs above the maximum effective dose of that given alone. The use of antidepressants and antiepileptics together would produce massive drowsiness. A drug interaction occurs either in the pharmacokinetic (PK) or the pharmacodynamics (PD) steps.

PK interactions occur during absorption, distribution, metabolism or excretion of drugs.

Absorption interaction. Two orally administered drugs may interact with each other resulting in decreased or increased absorption of one or both of them. The underlying mechanism can be attributed to the following:

- **Altered pH**, as some agents are absorbed at certain pH range. Example, would be ketoconazole which is absorbed better at low pH. So, the use of antacids is expected to lower its absorption rate
- **Chelation process** by multivalent ions to form insoluble complexes. For example, calcium decreases the effectiveness of tetracycline or ciprofloxacin
- **Effects on the GIT flora**. Some drugs (Digoxin) are inactivated by certain bacterial species in the large intestine. When co-administered with broadspectrum antibiotics, digoxin inactivation is reduced causing digoxin toxicity. Oral contraceptives, on the

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other hand, would loss effectiveness as the gut bacteria act on the conjugated form by hydrolyzing it and librating an active agent for intestinal re-absorption

- **Effects on GIT motility.** Delayed gastric emptying would delay drug absorption. Paracetamole absorption is increased by the use of metoclopramide which increases gastric emptying. Such effect is useful for treatment of migraine.

Distribution interactions. The active agent is distributed by binding to plasma proteins like albumin and α_1-acid glycoprotein. The bounded agent is unable to act on the receptor site but remains protected from metabolism or excretion. Some drugs, like NSAIDs, would displace oral anticoagulants from their plasma proteins, resulting in increased susceptibility to bleeding.

Metabolism interactions. Drug metabolism occurs in the liver, kidneys, GIT, lungs, placenta and even in skin. The process is divided into two phases, Phase I which involves oxidation, reduction and hydrolysis, and Phase II which involves conjugation. The cytochrome P450 isoenzymes are responsible for the process. A drug can be the substrate or the inducer/inhibitor of a CYP enzyme, or even both. Examples of known enzyme inducers include: Rifampicin, phenytoin, barbiturates and carbamazepine (able of autoinduction). The result of enzyme induction is decreased effects of the affected drug, except when the active agent is its metabolite. It is important to note that the mechanism of induction need time in order to synthesize new enzymes. Enzyme inhibitors, on the other hand, result in toxicity of the hypometabolized agent. Example of such inhibitors include: Agents with imidazole ring (ketoconazole, itraconazole, etc.), ciprofloxacin, erythromycin and propoxyphene. Another way of affecting drug metabolism is by affecting the hepatic blood flow. Propranolol decreases the cardiac output and reduces blood supply to the liver which affects lidocaine metabolism.

Elimination interactions. Drug elimination usually occurs by the renal system. Interactions at this level may be due to:

- Altered blood supply to the kidneys, which reduces the filtration rate. An example is indomethacin (NSAINs) which inhibits PG. This would affect the rate of lithium excretion causing lithium toxicity. Altered pH, which affects drug re-absorption from the renal tubules. pH affects the ionization of acidic or alkaline drugs. Weak acids become ionized and lipid insoluble when placed in

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alkaline media which prevents their re-absorption. The same goes for weak bases

- Affected active transport, which affects drug secretion. Active agents may have special mechanism for their secretion into tubule lumen and this can be the active transport system. When this system is occupied by another drug, for example ASA in case of methotrexate therapy, the result would be methotrexate toxicity. Another example of clinical benefit is the use of probecid which increases penicillin therapeutic effects

PD interactions occur at the receptor site. They are defined as the change drug actions regardless of the change in the amount available or the quantitative deposition. The two drugs are acting on the same receptor site or at the same system. The following are examples of PD interactions:

- The effect of sulfonylurea (agent used to promote insulin secretion by the pancreas) is decreased by the use of non-selective B blockers which block the B pancreatic cells
- The use of NSAIDs reduces renal blood flow and may result in Na and water retention. This antagonizes diuretics and ACEs (anti-hypertensive agents)
- The use of potassium sparing agents along with K supplements would lead to hyperkalemia.

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Chapter 2

Pain Control Medications in Dentistry

INTRODUCTION

Most of the times, the patients' main concern and chief complaint when they come to the dental clinics, is pain. It is pain that brings most of the hesitating patients to the dental clinics and keeps them away, too. Pain is unpleasant sensory and emotional experience that tells us about some sort of tissue damage that is occurring in the body. It is, however, considered as a normal physiological process. What characterizes dental pain is that it is usually severe and devastating. This is attributed to the fact that nerves are present between the solid walls of the tooth and when inflammatory edema collects, it finds no way of expansion and, rather, exerts more pressure on the nerve endings.

Whether this pain is pathological or an attempt to remove pathology, the patient is usually anxious about it. Identifying the source of pain can be a difficult task, however, an essential one to manage pain.

NEUROPHYSIOLOGY OF PAIN

Pain is received by the pain receptors "nociceptive receptors" at the free nerve endings. At the time of injury, fast/sharp pain is felt which is conducted by the myelinated A delta fibers. After the initial injury, the site of damage continue signaling about the damage occurred using the slow unmyelinated C fibers. Pain perceived at this time would be dull but continuous.

Pain waves travel through primary afferent neurons (A delta and C fibers); and via the dorsal root, they enter the spinal cord. This is the first order neuron and it synapses with the second order neuron that ascends through the spinothalamic tract to enter the thalamus. The thalamus, acting as the "gateway" of the brain, specifies the direction of the incoming of information. The third order neuron is directed from the thalamus to relay on the postcentral gyrus of the cerebral cortex. It is there where pain is localized and identified. Nerves communicate with each other by means of neurotransmitters as substance P and nitric oxide gas.

It should be noted that pain is associated with the production of several chemical agents within the body. These include prostaglandin, histamine, bradykinin, serotonin and potassium ions. They act as inflammatory mediators. Of special interest is prostaglandin. Injury to body cells results in the release of membrane phospholipids which are converted by phospholipase enzyme into arachidonic acid. Cyclooxygenase enzyme II (COX-2) acts on arachidonic acid to produce proinflammatory prostaglandins. Prostaglandins magnify pain by increasing the function of nociceptive receptors through a process known as sensitization.

Pain is normally associated with several reactions. Motor reactions initiate protective reflexes to avoid further damage to the tissues. Emotional reactions, on the other hand, express anxiety

and depression and record the event for future memorization. This is also a way of protection and prevention of damage at the future. Autonomic reaction is the translation of the event in terms of the body functions, exhibiting reaction to stress. The heart rate, blood pressure and metabolic rates are elevated.

In a way of protecting the body from excessive pain perception, the body produces what is known as endogenous opioid peptides namely enkephalin and endorphins. Enkephalins appear to be produced by the pregnant women during labor, whereas endorphins are produced by athletes during exercise to allow endurance and tolerance of hard work. Both act by preventing the release of excitatory neurotransmitters.

Pain is described regarding its severity or intensity into mild, moderate and severe. Being completely subjective, pain severity is difficult to be identified precisely. The final figure of pain is formulated and modified by several factors, the most important of which is the psychological state of the patient. It is well-known that stressful situations and psychological trauma aggravate or possibly induce pain.

Of interest in this chapter is to discuss pain in relation to its presentation during clinical examination (preoperative), during its treatment (operative) and after removal of the cause (postoperative).

CLINICAL PRESENTATION OF PAIN

Several diseases and conditions are associated with pain on clinical examination (Table 2.1). It should be emphasized that correct diagnosis is primary in order to eliminate the source of pain. Usually, the source of pain is obvious and related to some pathology. Some types of pain are deceptive, however. Of special interest is the referred pain. The secret behind pain referral lies in the fact that there is some sharing in the pathway of pain transmission (conversion-projection theory). According to the frequency of previous stimulation and experience, the brain assumes that pain is coming from that site, a process known as habit reference. If pain from inflamed maxillary sinus is misdiagnosed and treated by

Table 2.1: Conditions associated with orofacial pain

Intraoral painful conditions	*Extraoral conditions associated with pain*
Pulp conditions • Dentinal hypersensitivity • Pulp hyperemia • Pulpalgia (*mild*, *moderate*, *advanced*) • Periapical pathosis – *Acute apical periodontitis* – *Acute apical abscess* • Referred pulpal pain **Periodontal conditions** • Pericoronitis • Abscess of the periodontium – *Gingival* – *Periodontal* • Acute herpetic gingivostomatitis • ANUG • AIDs-associated NUP **Bone conditions** • Fractures • Acute osteomyelitis • Infected cysts • Sickle cell infarcts • TMJ disorders • Bone neoplasms **Salivary gland diseases** • Inflammatory disorders • Obstructive disorders **Conditions of the oral mucosa** • Ulcers (viral, fungal, traumatic, etc.) • Denture sore mouth • Remaining roots under dentures	**Referred pain from extraoral/ remote sources** • ENT diseases – *Sinus conditions (maxillary and paranasal)* – *Ear conditions* • Salivary gland diseases • Cardiac diseases – *Angina pectoris* – *Myocardial infarction* – *Carotidynia* • Cervical spine • Thyroiditis **Muscular disorders** • Myospasm • Myositis • Local unclassified myalgia • Myofacial pain **Neuropathic disorders** • Trigeminal neuralgia • Postherpetic neuralgia • Post-traumatic neuralgia • Glossopharyngeal neuralgia • Occipital neuralgia • Nervous intermedius neuralgia • Neuroma • Anesthesia dolorosa **Neurovascular disorders** • Migraine • Cluster headache **Vascular disorders** • Giant cell arteritis (temporal arteritis) • Hypertension **Atypical facial pain** • Atypical odontalgia • Burning mouth syndrome

restoring or extracting a maxillary tooth, the result will be more complications. Sometimes, referred pain may be an indication for patient referral to a specialist, as in case anginal, ENT, or thyroid pain. The dental evaluation may reveal nothing to be abnormal and accordingly the patient should be referred for further evaluation instead of blind treatment.

Pain from psychological source is another dilemma that may need the consultation of more than one specialty. Pain of this type is usually chronic and no obvious organic source is identifiable. However, some psychological problems may be identified. Patients may unconsciously substitute their psychological pains with somatic symptoms through what is called the conversion reaction. Comprehensive history taking is essential and the patient may need further psychological evaluation and management.

INTRAOPERATIVE PAIN

Usually, an operative or surgical procedure is required to treat pain. The methods by which pain is basically treated are listed in Box 2.1.

The nature of dental procedures requires the use of several cutting instruments and tools which are naturally pain producing. Pain may therefore be caused at least during the dental procedure

Box 2.1: Basic methods of pain management

- Identification and removal of the primary cause under effective pain control conditions
- Use of analgesics and anti-inflammatory drugs
- Counter-irritation and large fiber stimulation by the use of hot/coldpacks, rubbing, acupuncture, and electric stimulation of the periaqueductal gray matter
- Use of steroids to suppress severe inflammatory conditions
- Use of anticonvulsants and antidepressants
- Psychotherapy for cases originated from nonorganic sources; like atypical pain
- Surgical and ablative denervation operations, including neurectomy, dorsal rhizotomy, thalamotomy or even gyrectomy

Box 2.2: Different techniques used to manage operative pain

Topical anesthesia

Local anesthesia

- *Infiltration*
- *Nerve block*
- *Intraligamental*
- *Intrapulpal*
- *Electronic*

Sedation

- *Inhalational sedation* (NO_2)
- *Intravenous sedation*

General anesthesia

even when it was not the chief complain of the patient. This would necessitate some sort of anesthesia in order to make the procedure doable without risks or harms either to the patient or to the dentist. Different methods of pain control during the dental procedures are listed in Box 2.2.

Anxiety sometimes makes the dental treatment difficult if not impossible. It should be considered first as it may even obstruct the anesthetic procedure. All patients should be treated with mercy and handled with care and interest. Careful handling, good personality and other non-drug approach may help in managing mildly anxious patients. Sometimes, the patient is extremely anxious, very young or the procedure itself is extensive or long. Such situations may require the use of sedatives and anxiolytics (Table 2.2).

The use of topical anesthetics is indicated in minimal or superficial procedures, as these agents are effective in minimal depths (2–3 mm only). Therefore, they are useful in I and D, scaling and root planning and for painless needle insertion in case of local anesthesia. Topical anesthetics are supplied in spray, gel or ointment form with the anesthetic agent being lidocaine at most of the times.

Infiltration and **block** techniques are the most commonly used methods for most of the dental procedures. It is noteworthy to consider the type of the anesthetic used, and the presence of a vasoconstrictor (Table 2.3). The use of vasoconstrictor not only

Table 2.2: Common anxiolytics

	Dose
• **Short acting (3–8 hours)**	
Oxazepam	
Oxazine	10 mg
Triazolam	
Halcion	0.125– 0.25 mg
• **Intermediate acting (10–20 hours)**	
Lorazepam	
Ativan	1–2 mg
Temazepam	
Restoril	15 mg
• **Long acting (1–3 days)**	
Diazepam	
Valium	5–10 mg
Chlordiazepoxide	
Librium	5–10 mg

Table 2.3: List of anesthetic agents according to their duration of action

- **Short acting (less than 30 min)**
  - Prilocaine 4%, without vasoconstrictor
  - Lidocaine 2%, without vasoconstrictor
  - Mepivacaine 3%, without vasoconstrictor
- **Intermediate acting (60 min)**
  - Lidocaine 2%, with epinephrine 1/100,000
  - Mepivacaine 2%, with epinephrine 1/400,000
- **Long acting (more than 90 min)**
  - Bupivacaine 0.5%, with epinephrine 1/200,000
  - Prilocaine 4%, with epinephrine 1/200,000
  - Etidocaine 1.5%, with epinephrine 1/200,000

Box 2.3: Contraindications of vasoconstrictor

- History of allergy
- Uncontrolled hypertension
- Coronary heart disease
- Use of nonselective B-blocker
- Hyperparathyroidism
- Use of tricyclic antidepressants (doxepin)

prolongs the effects of local anesthesia, but also lessens the chance of systemic toxicity. In addition, it provides a clear field as a result of its hemostatic effects. Contraindications of the use of vasoconstrictors may exist, however, and should be avoided accordingly (Box 2.3).

It should be noted to the patient that not all sensations will be blocked out, and the feeling of pressure will persist. In some cases, pain is still present and may prevent further procedure, although the area is well anesthetized. This can be attributed to acute inflammation reaching the bone or due to interlacing nerve supply from adjacent nerves. The use of intraligamental or intrapulpal techniques may help in solving the problem of inflammation. The common interlacing nerves include nerve fibers crossing the midline and nerve fibers from the C2 and C3 area supplying the lower premolar area. Sometimes, anesthetic agent may not reach a flared palatal root approaching the midline in upper first molar. Pain would persist especially when working on that canal. In this case, palatal infiltration would help to solve the problem.

The use of **electronic anesthesia** solved the problem of needle phobia. It may alone allow for simple procedures or may be combined with nitrous oxide sedation or needle anesthesia. It offers a way of non-chemical way of controlling pain, therefore lesser risks of systemic toxicity or allergic reactions. In addition, it is a non-invasive method and this is advantageous to prevent the spread of infection as in case of abscess. However, this technique has its disadvantages and limitations (Box 2.4).

Box 2.4: The disadvantages and limitations of electronic anesthesia

- Tingling sensation
- Increased salivary flow
- No clear field as provided by VC
- Electric shock may occur when touching metallic instruments
- Not suitable for patients with pacemaker
- Not used in case of cerebrovascular disease or with brain tumor
- Not used in patients with bleeding disorders
- Not used in pregnancy

The famously known as "the laughing gas", *nitrous oxide* is a way to sedate and control pain (Stage I analgesia) in young, uncooperative or anxious patients. It produces Stage I analgesia and relaxes the patient, yet, not losing consciousness. The natural protective reflexes are not stopped and the patient is able to follow the operator's commands. The procedure involves the use of NO_2 gas plus oxygen mixed at the ratio of 50:50.

The patient's vital signs should be checked before the procedure and taken as a guide to confirm recovery after the procedure. At the end of the procedure, nitrous oxide is decreased to zero level and the patient should breathe pure O_2 for three to five minutes. Contraindications of nitrous oxide are listed in Box 2.5.

The use of *intravenous sedation* produces deeper Stage I analgesia and can be used for those who cannot use inhalational anesthesia due to breathing problems like mouthbreathing.

Sometimes, it is better to have the patient unconscious as in complicated and extensive cases. *General anesthesia* produces a reversible, controlled loss of sensations and consciousness; as well as, the protective reflexes. It passes through four stages, namely, analgesia, excitement, general anesthesia and respiratory failure.

Box 2.5: Contraindications of nitrous oxide

- 1st trimester pregnancy
- Conditions of difficult respiration
- Mouthbreathing
- Emphysema

Two dangerous states are the stage II, where unexpected movement of the patient may occur, and stage IV where the patient may go into coma. Respiratory and cardiovascular functions should be monitored throughout the procedure.

Induction of general anesthesia follows the administration of preanesthetic medication. It is started by the use of intravenous injection of sodium thiopental or methohexital. A mixture of gas, which contains enflurane, nitrous oxide and halothane, is used to maintain the state of general anesthesia.

POSTOPERATIVE PAIN MANAGEMENT

Dental procedures, whether to eliminate pain or not, are associated with some sort of body reaction and inflammation. The degree of inflammation and pain depends largely on the proper removal of the cause through proper diagnosis and treatment plan. The way the tissues were handled will be reflected postoperatively in terms of edema and pain. Table 2.4 lists some of the sources of pain occurring as a result of postoperative complications. Useful operative guidelines regarding postoperative pain reduction are listed in Box 2.6. So much can be done during the dental procedure to minimize postoperative pain and inflammation. The use of light, intermittent touching, as well, as copious coolant during caries removal ensures little or no injuries to the dentinopulpal organ. The use of sharp instruments eliminates the need for pressure and, hence, burs should be changed whenever the need to exert pressure is felt. Unnecessary overextension also takes part in the compromise on the pulp tissue. Care must be practiced also during application of rubberdam clamp, matrices and gingival retraction cords as innocent adjacent tissue do hurt when anesthesia wears off after the procedure. The value of the procedure equals nothing if the material used to restore the prepared cavity is irritating or not in harmony with normal occlusion. The patient will only complain of pain, although might be of different origin.

Surgical procedures should follow the principles of surgery and be as traumatic as possible. Aseptic and clean field must be

Table 2.4: Possible sources of postoperative pain

Source of pain	*Possible causes*
Dentinal hypersensitivity	Moisture contamination during amalgam placement Microleakage Overzealous finishing at cervical margin
Pulpitis	Microleakage Failure to provide temporary filling or crown Poor thermal and chemical insulation Iatrogenic exposure of the pulp of vital tooth
Dry socket (alveolalgia)	Increased fibrinolytic activities possibly due to bacterial infection Excessive tissue manipulation during extraction Excessive use of vasoconstrictor Failure to form and maintain stable blood clot possibly due to insufficient postextraction instructions or poor patient compliance Patient systemic background indicates poor blood supply (e.g. smoking and radiotherapy)
Traumatic neuroma	Trauma to nerve Curetting nerve ending after extraction
Periodontal abscess	Incomplete calculus removal Perforation during root canal treatment
Periapical periodontitis	Overextension during RCT Overfilling of GPP Traumatic occlusion or high spots
Trismus	Injecting into the medial pterygoid muscle Muscle fatigue due to prolonged mouth opening throughout the procedure without the use of mouth probe
TMJ pain	Poor occlusal relation Failure to support the mandible during extraction

Box 2.6: Basic operative guidelines to minimize postoperative pain

- Correct diagnosis and proper treatment plan
- Proper use of instruments
- Atraumatic operative procedure as possible
- Avoid injury to innocent adjacent tissue
- Complete removal of the cause
- Adequate postoperative care
- Adequate postoperative instructions

maintained through the procedure. Instruments should be used in the proper way, they were designed to. Injudicious use of these instruments may cause injury to adjacent soft tissue, vital structure or may even complicate a procedure which might be simple just if the right instrument used in the right way. Excessive tissue manipulation, excessive force and excessive removal of bone all account for the degree of swelling and pain and the rate of wound healing after the surgery. Sometimes, however, it is better to remove some bone around a tooth which is to be extracted than to try extracting it by the closed method. This could save time, effort and may in fact spare the patient from further complications. This makes a recall to consider the significance of proper diagnosis and treatment planning.

Irrigation, debridement and inspection of the surgical field before suturing are all important steps. Suturing, too, must be done in a proper way to prevent the possibility of complications after the surgery.

Adequate postoperative instructions and care are of great importance in completing the treatment and for the comfort of the patient. The patient should be told about possible pain and discomfort that may occur after the procedure and what to do about it. This would save much of the patient's effort in worrying about what is going on. Usually, postoperative instructions are given to provide care and avoid irritation. They should be provided verbally and in the written form. Making the patient participate in the management of pain and swelling after the procedure provides

the patient with sort of relief. Holding icepacks for 20 min/hour after surgical procedures and hot one, two days after, really helps the patient control edema and have some sort of pain relief. Analgesics and anti-inflammatory drugs should be prescribed in a proper way and their significance should not be overlooked. These drugs may help the patient perform daily activities normally, that is, to sleep well, eat normal diet and be psychologically comfortable.

DRUGS FOR PAIN RELIEF

The next section is an overview of the drugs that can be used to relief pain, usually postoperative, and control inflammation (Box 2.7).

Box 2.7: Commonly used analgesics and anti-inflammatory drugs

Nonopioids
Paracetamol
NSAIDs
- **Nonselective COX inhibitors**
  Aspirin (ASA)
  Ibuprofen
  Ketoprofen
  Fenoprofen
  Diclofenac
  Ketorolac
- **Selective COX-2 inhibitors**
  Celecoxib
  Rofecoxib
  Valdecoxib
  Parecoxib
  Etoricoxib
- **Opioids**
  Codeine
  Propoxyphene
  Oxycodone
  Hydrocodone
  Hydromorphone
- **Steroids**
  Hydrocortisone
  Prednisone
  Triamcinolone
  Betamethasone

Nonopioids

Paracetamol (Acetaminophen)

Paracetamol is a mild analgesic, antipyretic, but poor anti-inflammatory. It is the safest drug and should be considered first. It is used to alleviate mild-to-moderate pain in inflammation-free conditions. It is available in tablets and syrups. Paracetamol is also useful in case of moderate-to-severe pain in combination with opioids. The drug acts by inhibiting central prostaglandin via inhibition of cyclooxygenase enzyme. It also acts by inhibiting nitric oxide gas which is important for communication between nerve cells. However, this gas is also important for sexual arousal, and blood pressure modulation. The usual dose of paracetamol is shown in Table 2.5. Because it is metabolized in the liver, paracetamol should be avoided in case of liver disease and alcohol consumption.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

This group of drugs is chosen for mild-to-moderate pain and helpful in conditions associated with inflammation. They act by non-selective inhibition of all COX enzymes. However, due to the side effects of such inhibition, a newer group of selective COX-2 inhibitors was developed. It should be noted that there are three categories of cyclooxygenase enzyme with three types of prostaglandin synthesized by their action (Table 2.6).

The members and dosages of nonspecific NSAIDs are listed in Table 2.7. **Aspirin** (acetyl salicylic acid or ASA) is the mildest agent and is of comparable analgesic effects to paracetamol. However, it has greater anti-inflammatory component as it acts by nonselective inhibition of cyclooxygenase enzyme both peripherally and centrally. Aspirin, like other members of NSAIDs, inhibits the normal function of platelets by inhibition of thromboxane A2 which is

Table 2.5: Dosage of paracetamol for both children and adults

Panadol/Adol	*Dose (mg)/6–8 h*	*Maximum dose/day*
Adults	500–1000	4000
Children	10–15 mg/kg	65 mg/kg

Table 2.6: Types and functions of cyclooxygenase enzymes and prostaglandins

	Trigger of release	*Type of PG produced*	*Function*
COX-1	Normally in the kidneys, platelets and GIT mucosa	House-keeping prostaglandins	Normal renal circulation Platelet aggregation Normal gastric lining
COX-2	Damage to cells Cytokines prostaglandins	Proinflammatory prostaglandins	Pain and inflammation
COX-3	Late stage of inflammation	Anti-inflammatory prostaglandins	Suppresses inflammation and allows repair

Table 2.7: Dosage and maximum daily dose of nonspecific NSAIDs

	Dosage (mg)	*Maximum daily dose (mg)*
Aspirin (ASA) **Dipirin** **Biospirin**	650–1000/6 h	4000
Ibuprofen **Ulrafen** **Cetafen†**	200–800/6 h	2,400
Fenoprofen	300/6 h	300
Ketoprofen **Osthofen**	25–50/8 h	300
Diclofenac Na Voltaren Resinate*	50–75/8 h	200
Diclofenac K Cataflam **Olfen**		

Contd...

Contd...

Etodolac **Etodine** **Napilac**	200–300/8 h	1000
Ketorolac **Ketorol** **Torolac**	10/6 h	1200

† With paracetamol
* With cholestyramine

important for their aggregation. This inhibition appears to be reversible in 24 hours with all members of NSAIDs except aspirin. Therefore, the normal function of platelets is lost irreversibly and the function can only be resumed when new ones are produced in about 11 days. Special consideration should be made before prescribing aspirin regarding the tendency towards bleeding. Possible adverse reactions and contraindications to NSAIDs are listed in Table 2.8.

Ibuprofen is a stronger and more effective agent in diminishing pain and inflammation when compared to ASA. It was reported that it is as effective as the combination between paracetamol and an opioid, therefore, should be tried first in case of moderate-to-

Table 2.8: Side effects and associated contraindications of NSAIDs

Adverse effect	*Contraindication*
Gastric irritation	Stomach ulcers
Bleeding tendency	Bleeding disorders
	Anticoagulant therapy
	Third trimester pregnancy
	Alcohol consumption
Impairment of renal functions	Severe renal disease
Allergic reactions	Asthmatic patient
	History of hypersensitivity to any NSAIDs
Hemolysis in case of G6PD deficiency	G6PD deficiency

severe pain. The combination between ibuprofen and paracetamol (600 mg + 1000 mg/6 h) was reported to be a good pain killer in case of endodontic pain.

The use of selective NSAIDs helps avoiding the unnecessary inhibition of the normal functioning prostaglandins and hence lesser complications. They need lower doses as they have greater selectivity for COX-2. Rofecoxib 200 mg is comparable to ibuprofen 400 mg minus the irritating effects on the gastric mucosa. Table 2.9 shows the recommended dose of the COX-2 specific inhibitors. Due to inhibition of COX-2, however, prostacyclin and inflammatory prostaglandins are inhibited. Prostacyclin is believed to act by preventing platelet aggregation and hence, thrombosis. Blocking only COX-2, these selective inhibitors cause relative increase in the thromboxane A2 enzyme which may predispose to thrombosis. Rofecoxib has been withdrawn worldwide in 2004 due to its side effects on the cardiovascular system. Therefore, what remains of this group is contraindicated in patients with cardiac and vascular background. The decision between selective and non-selective NSAIDs is, therefore, made on the basis of GIT and CVS condition.

Opioids

Opioids are *strong analgesics* used to manage moderate-to-severe pain. They act by elevating the pain threshold on the cortical center and thalamus. They also interrupt the polysynaptic spinal pathway just like the internal morphine-like substances (endorphins and encephalin) by binding to opioid receptors. They are considered as the next level to treat pain that does not respond to NSAIDs.

Table 2.9: The dose of selective COX-2 inhibitors

	Dosage mg/24 h	*Maximum daily dose (mg)*
Celecoxib **Celebrex** **Eurocox**	100–200	400

However, these drugs should be used as adjuvant only and not relied on completely. Most of the times, opioids are mixed with acetaminophen or ASA. The nonopioid part should be of higher dose and only the minimal effective dose of opioids should be used. This would help in decreasing the unwanted effects of opioids. The minimal dose of nonopioid part should be at least 650 mg as pain is usually more sensitive to that part (Table 2.10). Table 2.11 summarizes the unwanted effects of opioids and their causes. Attention should be paid to their contraindications, especially those with respiratory disease as they result in respiratory depression which may aggravate the existing condition. Narcosis, addictions and tolerance are possible results of their abuse. Tolerance is the need to increase the dose of the drug in order to reach its therapeutic effects. Opioids use is associated with constipation due to inhibited bowel movement. Their administration may requires the prescription of a laxative, especially when the patient is suffering from previous constipation.

Steroidal Anti-inflammatory Drugs (SAIDs)

Steroids, mainly cortisole, are the group of corticosteroids normally secreted by the adrenal cortical gland. Normally, they inhibit inflammation, allow the body to cope with stress and ensure the

Table 2.10: Opioids used in pain management in order of their strength

Opioid	*Dose (mg)*	*With acetam*	*With ASA*
Codeine	30–60	**Tylenol**	**Empirin**
Propoxyphene	100	**Darvocet**	**Darvon**
Hydrocodone*	5–10	**Lorcet**	**Lortab ASA**
Oxycodone	5–10	**Percocet**	**Percodan**
Hydromorphone	2–4	Used only in severe cases for the shortest possible time and shortest duration	
Morphine	10–15	Used in severe cases	

* Present also in combination with ibuprofen as vicoprofen.

Table 2.11: Unwanted effects of opioids

Adverse effects	*Cause*	*Contraindication/ caution*
Respiratory depression	Inhibition of respiratory center	Chronic respiratory diseases
Hypotension	Inhibition of vasomotor and cardiovagal centers	
Hypothermia	Inhibition of heat regulation center	
Allergy	Histamine release	Avoid in history of allergy May be replaced by totally synthetic groups as meperidine
Tolerance **Physical dependence** **Addiction**	Inhibition of frontal area	Avoid abuse Avoid long-term use
Constipation	Decreases propulsive movement of GIT	Avoid in case of inflammatory bowel disease Patient may need laxative especially if already constipated
Nausea and vomiting	Stimulation of chemoreceptor trigger zone	Patient should be informed to lie down and rest
Mode alteration (euphoria/dysphoria)		Avoid in emotionally unstable patients Patient should be informed of such effect

effective actions of other hormones. Its secretion is triggered by the ACTH from the pituitary gland.

Their effects on inflammation is broader than NSAIDs, as that they inhibit the whole inflammatory cascade by inhibition of the synthesis of arachidonic acid from membrane phospholipids.

This is achieved via the inhibition of phospholipase A2 enzyme. This would include the inhibition of all prostaglandins, as well as, leukotrienes which are involved in allergic reactions.

Use of steroids is the final choice to control edema and pain when other means of pain control have failed. Their uses are summarized in Box 2.8. They are available in topical form, as well as oral and parenteral ones.

Box 2.8: Indications of steroids

- Emergencies
  - *Adrenal crisis*
  - *Anaphylactic reactions*
  - *Severe infections*
  - *Severe trauma*
- Severe postoperative swelling
- Severe myositis or TMJ dysfunction
- Mucosal lesions and ulcerations, as in:
  - *Recurrent aphthous ulcers (RAS)*
  - *Lichen planus*
  - *Pemphigus vulgaris*
- Neuralgic pain, as in:
  - *Trigeminal neuralgia*
  - *Postherpetic neuralgia*
  - *Glossopharyngeal neuralgia*

It should be noted that patients on prolonged steroids therapy are associated with adrenal dependence and the dose should be altered before and after the provided treatment. Common side effects of steroids are summarized in Table 2.12.

Adjuvant Analgesics

Drugs other than those described in this chapter may also be used to treat certain types of pain, although their main use is not so. Anticonvulsants, as carbamazepine and dilantin, may be the only drugs that resolve neuralgic pain. They are used in increasing doses starting by 100 mg and may reach 800 mg/day.

Table 2.12: Effects and cautions/contraindications of steroid use

Effect	*Caution/contraindication*
Anti-inflammatory and antiallergic with immunosuppressive effects	Avoided in case of infections (Reye's syndrome)
Diabetogenic and anti-insulin effects	Not used for diabetics
Catabolic effects by prevention of formation of proteins	Wasting muscle disease
Affects fat distribution	Moon face and buffalo appearance
Antidiuretic effect mimicking aldosterone	Not indicated for hypertensives or hypokalemics
Osteoporosis of bone	Increased susceptibility to bone fracture
Increases secretion of gastric HCl and pepsin	Avoided in patients with peptic ulcer. Caution on other drugs that cause gastric irritation like NSAIDs
Psychosis	Avoid in psychic patients

Antidepressants, as doxepin, may also be used to treat neuralgic pain, burning mouth syndrome, TMJ dysfunction syndrome and atypical facial pain.

Ergotamine is derived from ergot and it is used for its vasoconstriction effects. It is used to treat migraine and cluster headaches. It is also used in initiation of labor.

Topical Agents

Agents to manage dentinal hypersensitivity primarily aim to block the dentinal tubules by forming an insoluble plug or by stimulating irritation dentin to form. These agents can be self-applied or professionally-applied. Table 2.13 lists the various methods used to treat dentinal hypersensitivity.

Topical preparations are also available for local control of pain and inflammation (Table 2.14). Usually; topical analgesics are used for oral ulcers which can be quite painful. By minimizing pain,

Table 2.13: Techniques of managing dentinal hypersensitivity

Toothpastes	**Strontium chloride (Sensodyne):** Reacts with phosphate in dentinal fluid to form strontium phosphate crystals which act by blockade of dentinal tubules **Potassium nitrate 5% (Sensodyne):** Act as above, but with additional desensitization of dentinal mechanoreceptors
Topical fluoride	**Sodium fluoride 33%*** Fluoride act by forming fluorapatite crystals with calcium
Potassium oxalate	Reacts with calcium ions to form calcium oxalate crystals
Dentin bonding agents	Provide a protective coating over the open dentinal tubules

* May require more than one application

Table 2.14: Topical agents used to reduce pain from oral ulcers

Action	*Agent*
Analgesics/anti-inflammatory agents	**Choline salicylate** (gel; **Mundisal)** **Lignocaine** (gel; **Jogel)** **Benzydamine** (MW; **Tantum Verde)**
Covering agents	**Carboxymethylcellulose** (paste; **Orabase)***
Antiseptic agents	**Chlorhexidine** (MW; **Hexitol**, **Citrolin F**, **Septoral)** **Tetracycline (MW)**

* Triamcinolone 0.1 percent may be included

the patient health is improved which further allows better healing. Some agents work by direct application of analgesic agents (choline salicylate, lignocaine or benzydamine).

Others allow for healing either by providing a protective covering (Orabase) or by inhibiting secondary bacterial infections (chlorhexidine). Corticosteroids can also be included in some preparations.

GENERAL CONSIDERATIONS

Sufficient doses of anti-inflammatory drugs may be used during the operation or shortly after in order to counteract the production of prostaglandin. This will help in starting the analgesic effect of the drug before the anesthesia wears off, thus ensuring comfort of the patient. Some would advice the injection of Voltaren all around the surgical site in order to inhibit the production of prostaglandin and to minimize postsurgical edema and pain.

The drug should be used in regular intervals, every six to eight hours, rather than postprandial or "as required". This ensures sufficient and continuous action.

As the area of inflammation starts to heal and pain comes under control, it is advisable that the use of anti-inflammatory is discontinued to avoid inhibition of COX-3 which produces anti-inflammatory prostaglandin that helps in the repair process.

SPECIFIC CONSIDERATIONS

Certain agents should not be used in certain conditions. Table 2.15 lists the drugs that can be used safely during pregnancy and

Table 2.15: Specific considerations regarding anxiolytics, local anesthetics, and analgesics

Anxiolytics

- Avoid all in both pregnancy and breastfeeding as they can cross the placenta and appear in milk, which consequently affect the fetus. Depression of respiration or CNS may also occur
- Nitrous oxide can be used in the 2nd or 3rd trimesters, however, with care

Local anesthetic agents

Pregnancy		Breastfeeding
Use	**Use with caution**	
Lidocaine	Mepivacaine	All agents can be used safely
Prilocaine	Bupivacaine	
Benzocaine	Articaine	
Epinephrine		
Vasoconstrictor		

Contd...

Contd...

Liver failure	
Use	**Avoid**
Prilocaine	Lidocaine
Articaine	Mepivacaine
	Bupivacaine

Analgesics and anti-inflammatory agents

Pregnancy			**Breastfeeding**	
Use	**Use with caution**	**Avoid**	**Use**	**Caution**
Acetaminophen	Aspirin	*Aspirin* or	Acetaminophen	Aspirin
	Ibuprofen	*ibuprofen* in	Ibuprofen	Indomethacin
	Rofecoxib	the 3rd	Diclofenac	Cortisone
	Codeine	trimester	Codeine	
	Hydrocodone		Propoxyphene	
	Oxycodone		Hydrocodone	
	Propoxyphene		Oxycodone	
	Corticosteroids			

Liver disease/failure	Most agents are metabolized in liver and
Kidney disease/failure	excreted by the kidneys, so in the presence of disease, the dose and/or duration should be adjusted to avoid toxicity

breastfeeding and those that should be avoided. In addition, those agents metabolized in the liver and excreted by the kidneys, may, in

Box 2.9: Drug interaction

The concurrent administration of two drugs may affect the availability of one or both, thereby, affecting the therapeutic benefits. However, the reaction can be quite dangerous, too.

The use of the **vasoconstrictor** "epinephrine" in the local anesthetic solution may cause fatal hypertension in patients who take nonselective B-adrenergic antihypertensive drugs (Nadolol and propranolol are examples). Such effect may occur as these drugs block both B_1 and B_2 receptors. B_1 adrenergic receptors are cardioreceptors responsible for the increase of cardiac output while B_2 act peripherally by dilating blood vessels especially in the muscles, which provides a compensating action to counteract the increased blood pressure. Blocking both receptors by the nonselective B-blocker agent causes

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adrenaline to be directed to α-receptors that work by vasoconstricting peripheral arterioles and hence, high blood pressure.

Cholestyramine (antihyperlipidemia drug) may interfere with the absorption of **acetaminophen**, so it should be taken 3 to 4 hours before paracetamol. Paracetamol is primarily metabolized in the liver. The concurrent administration with a hepatic enzyme inducer drugs as tegretol, carbamazepine, rifampin and isoniazid, may reduce the effects of paracetamol as its metabolism will be increased. Its dose may need to be adjusted.

Alcohol use along with any drug metabolized in the liver increases the risks of liver damage. The administration of **aspirin** and live viral vaccine (varicella zoster vaccine) or in the presence of infection may lead to Reye's syndrome. So, aspirin should be avoided for at least 6 weeks. Aspirin also may potentiate the effects of alcohol by increasing the possibility of gastric bleeding. It was reported that the effect of aspirin may be reduced if coadministered with ibuprofen, an effect which may necessitate delaying ibuprofen 30 minutes after aspirin or 8 hours before. Its administration with ketorolac is contraindicated as this combination is associated with increased tendency towards gastric bleeding and hemorrhage. The effects of warfarin (anticoagulant) and oral hypoglycemic were potentiated when used along with aspirin. Other drugs that may get potentiated if administered with ASA include phenytoin, valproic acid (anticonvulsant), thiopental (ultra short acting barbiturate) and thyroxin hormone.

Other NSAIDs may interfere with excretion of lithium (antipsychotic/antimanic), methotrexate (for rheumatoid arthritis and psoriasis) and aminoglycosides leading to their toxicity. They also participate in increasing the effects of anticoagulant drugs. The effect of antihypertensive drugs appear to be reduced possibly due to the inhibition of prostaglandin which may have a role in regulation of blood pressure. **Celecoxib** acts by inhibiting hepatic enzymes and this may lead to increased level of these drugs metabolized in the liver as β-blockers, antidepressants and antipsychotic. If co administered with aspirin, the risk of gastric ulcer is increased. Fluconazole antifungal may increase the blood concentration of celecoxib as it may reduce its hepatic elimination.

Opioids should not be administered with drugs that slow brain functions (as alcohol, barbiturates, and muscle relaxants) to avoid the

Contd...

Contd...

potential risk of CNS and respiratory depression which can be dangerous.

Carbamazepine and phenytoin are enzyme inducers which increase the rate of opioid metabolism. In the opposite, quinidine antiarrhythmic agent is enzyme inhibitor and may cause toxicity of opioid. Opioids may cause severe constipation if given along with antidiarrheal due to the added constipation effects.

Corticosteroids may lead to spread of infection, so should be avoided in episodes of infection and after liveviral immunization. The effects of diuretics can be counteracted by cortisole as it causes salt and water retention. Cortisone also counteracts the effect of hypoglycemic agents as it possesses a hyperglycemic effect. Enzyme inducers also cause increased cortisol elimination.

case of kidney and/or liver failure result in toxicity. These agents may be replaced or their dosage modified.

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Chapter 3

Antimicrobial Agents Used in Dentistry: Bacterial Infections

INTRODUCTION

Microorganisms, when they gain entry into the body, may be able to cause infections. Although, the main tool of the dentist is surgery,

anti-infective agents are sometimes necessary. Because dentists are prescribers, a thorough knowledge about microbiology, pathology and pharmacology is a must. Indiscriminate drug use may lead to variable risks ranging from increased burden on the body organs; liver and kidneys, to more serious complications as drug interactions and allergies. Therefore, a dentist should also know when to provide these agents and what precaution he might need to make. In this chapter, bacterial infections and the most commonly used antibiotics are of interest. Antifungal and antiviral agents are discussed in Chapter three and four, respectively.

BACTERIAL INFECTIONS

Most orofacial infections are mixed in nature, being associated with aerobic and anaerobic bacteria of both gram-positive and gram-negative species (Box 3.1). Although established infections are primarily anaerobic, it appears that anaerobic bacteria proliferate later as the aerobic species result in reduced oxygen environment. This is important as the choice of antibiotic may change regarding the stage of the infection.

For an infection to get established, bacteria of sufficient virulence and number should gain entry into the body tissues, a

Box 3.1: Most prominent bacteria in odontogenic infections

Aerobic
Gram (+) ive
Cocci*—*Streptococci/Staphylococci spp.
Rods*—*Corynebacterium spp.
Gram (–) ive
Cocci*—*Neisseria spp.
Rods*—*Haemophilus
Anaerobic
Gram (+) ive
Cocci*—*Streptococcus/Peptostreptococcus
Rods*—*Lactobacillus/Actinomyces
Gram (–) ive
Cocci*—*Veillonella spp.
Rods*—*Provetella/Porphyromonas spp.

process known as invasion. This would mean alteration in the balance among the normal flora or an introduction of bacteria foreign to the site of infection. Virulent factors enable bacteria to induce tissue inflammation and damage by several ways. This includes their ability to adhere and produce enzymes and toxins. The body, in a way to resist such insults, reacts by an inflammatory process. Inflammation is triggered either by the damaged cells or by the bacteria toxins. Of particular interest are endotoxins, which are the lipopolysaccharide part of gram-negative cell wall elaborated whenever the bacterial cell undergoes division or disintegration (death). Endotoxins cause the release of chemical mediators of acute inflammation, as IL1, from macrophages and other cells, inducing fever and hypotension.

The role of bacterial enzymes also takes part in the inflammatory process, as well as the final clinical appearance of the infection. Collagenase producing bacteria, as *Streptococcus*, are associated with spreading infections like cellulitis and facial space infections, whereas coagulase-producing *Staphylococcus* infections produce a localized abscess or infection. Although, this effect is of favorable appearance to the clinician, it is produced in a way to protect the focus of infection from the immune response. In these localized infections, incision and drainage is the best way to allow blood circulation and immune elements to reach the site of infection.

ANTIBIOTICS

Antibiotics are used to augment the body immunity to eradicate the infection or prevent the condition from becoming worse. Life-threatening conditions, like Ludwig's angina, may arise from dental infections. Bacterial endocarditis is another example of life-threatening infection-related to dental procedures, although the role of the dentist is actually preventive.

The ideal use of antibiotics should be directed to the precise causative organism with the narrowest spectrum possible. However, most dental infections are treated on presumptive basis with the choice of empirical antibiotics. Precise determination of the causative

microorganism is achieved by the procedure of culturing and the most effective antibiotic is determined by the sensitivity tests. However, this seems impractical as most infections get better if not resolved by the time, the results of culture and sensitivity tests show. So, the use of culture and sensitivity tests is reserved for more serious or rapidly progressing conditions and for those recurring or resisting treatment. Conditions of compromised host defense also indicate the use of culture and sensitivity tests.

Antibiotics work on basis of selective toxicity which means that antibiotics are toxic only to the organisms they were aimed to. However, this appears to be relative as some actions can be exerted on the body. Therefore, antibiotic risks should be kept in mind whenever prescribed and balanced against the benefits it may produce (Box 3.2).

Mechanism of Action

A common classification of antibiotics is based on their mechanism of actions (Table 3.1). Antibiotics are also described according to their final effect on bacteria as bactericidal (rapidly killing as the β-lactam group) or bacteriostatic (inhibiting like macrolides,

Box 3.2: Major risks of antibiotic use

Allergic reactions ranging from severe anaphylactic reactions to simple rashes
Gastrointestinal irritation like nausea, vomiting, diarrhea and abdominal pain
Hepatotoxicity affecting liver functions
Nephrotoxicity affecting renal functions
Ototoxicity due to accumulation in the perilymph and endolymph of inner ear
Superinfections as candidiasis and pseudomembranous colitis; mainly due to alteration of the normal flora
Drug interactions see the interaction box
Drug resistance where the drug is no longer effective on certain microorganisms

Table 3.1: Mechanism of action of most commonly used antibiotics

Mechanism of action	*Group*
Inhibition of cell wall synthesis	β-lactam group
	Penicillins
	Cephalosporins
	Glycopeptides
	Macrolides
Inhibition of protein synthesis	Lincomycins
	Tetracyclines
	Aminoglycosides
Interference with DNA	Nitroimidazoles
	Fluoroquinolones

tetracyclines and lincomycins). Whenever possible, bactericidal antibiotics should be used.

Inhibitors of the Bacterial Cell Wall Synthesis

These are bactericidal agent called the β-lactam group. The bacterial cell wall is the organelle responsible for the protection against environmental changes, mainly the osmotic pressure. It is composed of cross-linked peptidoglycans and the cross-linking appears to play a major role in its rigidity. β-lactam antibiotics bind to the penicillin binding proteins (PBPs) present on the surface of the cell wall. The process of transpeptidization is inhibited and the cross-linking process is stopped. In addition, these antibiotics act by the release of autolysin enzymes, by inhibiting their inhibitor enzymes. Autolysins take part in the remodeling process of the bacterial cell wall, a process that loses control when the responsible controlling enzyme is inhibited.

Inhibition of Protein Synthesis

Antibiotics of this group are the macrolides, tetracyclines, aminoglycosides and the lincomycins. All are bacteriostatic; although bactericidal in high concentration. Bacterial ribosomes are the organelles responsible for protein production under the control of bacterial DNA and RNA. These ribosomes are made of two subunits

30S and 50S, collectively known as 70S. Some antibiotics act by binding to the 30S (as tetracycline and aminoglycosides) while others act on the 50S (like macrolides and lincomycins).

Aminoglycosides block the protein synthesis process by binding to receptor P12 present on the 30S subunit. Consequently, protein synthesis is blocked in addition to misreading of the mRNA and, hence producing non-functional proteins. Some actions also can be exerted by disruption of polysomes, a strand of ribosomes that read a specific mRNA to produce proteins. Tetracyclines, on the other hand, act by preventing the attachment of tRNA. Macrolides and lincomycins act similarly, by blocking the attachment of tRNA to ribosomes. Macrolides bind to receptor 23S rRNA present on the 50S.

Inhibition of Nucleic Acid Synthesis

Quinolones and nitroimidazoles **(Flygel)** are two bactericidal agents which act by interrupting bacterial DNA. Quinolones act by inhibiting bacterial gyrase, an enzyme responsible for unwinding the DNA before its replication, thus interfering with bacterial replication. Metronidazole, on the other hand, combines with bacterial macromolecules, producing DNA dysfunction and structural defects.

SYSTEMIC AGENTS

The following section is a brief description of the most commonly used agents in the management of orofacial infections.

Penicillin

Penicillins are the most commonly and safely used antibiotics. Their natural origin is from the mold *Penicillium notatum*. Penicillins act by inhibiting the bacterial cell wall synthesis and are bactericidal in action. Members of pencillin group are listed in Table 3.2.

Natural penicillins are mainly **penicillin G** (benzyl P) and **penicillin V** (phenoxymethyl P). Penicillin G is active mainly on gram-positive bacteria and some gram-negative ones. Parenteral

Table 3.2: Members of the penicillin group, route of administration and dosage

Members	*Route*	*Dosage*
Penicillin G	IV, IM	10^6 IU /qid
Penicillin G		
Ampicillin	O, IV, IM	500 mg/qid
Ampicillin		
Farcocillin		
Ampicillin-Sulbactam	O, IV, IM	375 mg/bid
Unictam		
Amoxicillin	O, IV, IM	500 mg/qid
Amoxicid		
Amoxil		
Amoxicillin-clavulanate	O, IV, IM	1g/bid
Augmentin		
E-moxcav		
Hibiotic		
Cloxacillin-Ampicillin	O, IV, IM	500 mg/qid
Ampiclox		
(250+250)		

administration ensures adequate concentration and thus, this agent is reserved for severe cases and cases where parenteral route is indicated. Penicillin V is more stable in gastric environment than penicillin G and, thus, is present in the oral form. Both have similar spectra, with more action on gram-negative bacteria by the PG form.

Amoxicillin, an agent of the aminopenicillin group, have extended spectrum over the natural penicillins on the gram-negative bacteria, but of lesser effects on the gram-positive ones. It is considered one of the safest and most commonly used agents. It is well-absorbed orally and provides good tissue distribution. β-lactamase inhibitors like sulbactam, tazobactam or clavulanic acid act by increasing the spectrum of penicillins and by resisting

β-lactamase enzyme. These resistant strains may inactivate β-lactam antibiotics by breaking the β-lactam ring converting them into penicilloic acid which is the inactive form. **Ampicillin** is another aminopenicillin but with more activity on the gram-positive bacteria. Penicillinase-resistant penicillins, like cloxacillin and dicloxacillin, are resistant to the enzymes produced by resistant strains.

Resistance to penicillin by the following bacteria is documented: *Veillonella*, *prevotella, denticola*, *S. mitis*, *S. oralis*, *S. salivarius* and *Fusobacterium*. Resistance is due to the production of β-lactamase enzymes, absent PBPs or decreased intrabacterial concentration of the drug either by decreased permeability or increased efflux.

Penicillins are excreted by the renal system, so care should be practiced in patients with renal problems.

Common adverse effects of penicillins include GIT troubles (nausea, vomiting, diarrhea), allergy to the β-lactam ring, and superinfection (candidiasis or pseudomembranous colitis). Cationic toxicity (with benzyl penicillin) may occur due to the addition of sodium or potassium, an effect that can be avoided by providing a stronger agent with lesser dose and frequency. Other effects include nephrotoxicity and neurotoxicity.

Cephalosporins

Cephalosporins are naturally derived from the Fungi *Cephalosporium*. They share similar properties with penicillins as they have the same β-lacatam ring in their structure and, too, bind to the PBPs. Accordingly, similar spectrum is anticipated, as well as, similar adverse reactions like allergy and resistance.

Cephalosporins are divided into generations according to the spectrum of their activity. First generation act on both gram-positive and negative bacteria and, hence they are the most useful agents. Second and third generations act more on gram-negative bacteria and their use in dentistry may be based on culture and sensitivity tests, as in resistant or refractory infections. A fourth generation was also developed, but its use is mainly restricted to those strains

Table 3.3: Members of cephalosporins, route of administration and dosage

Members	*Route*	*Dosage*
First Generation		
Cephalexin	Oral	250–500 mg/tid
Keflex		
Neocef		
Cefadroxil	Oral	500 mg/bid
Duricef		
Curisafe		
Second Generation		
Cefuroxime	O, IV, IM	250 mg/bid
Cefumax		
Hebiuroxime		
Cefaclor	O, IV, IM	250–500 mg/tid
Serviclor		
Third Generation		
Cefixime	Oral	200–400 mg/oid
Ximacef		
Cefotaxime	IV, IM	250–500 mg/bid
Cefotax		
Claforan		
Fourth Generation		
Cefepime	IM, IV	500 mg/bid
WinCef		
Maxipime		

resistant to the 2nd and 3rd generation. Table 3.3 shows common agents of cephalosporins and their doses.

Like penicillins, cephalosporins are also excreted by means of the renal system and should be provided with care in renal patients.

Common adverse effects are similar to those of the penicillin group. History of allergy to penicillin indicates possible allergy to cephalosporins and should be avoided accordingly. GIT troubles and superinfections are also possible. Increased bleeding tendency may be associated with agents that have the tetrazole ring in their structure; like **cefuroxime.** The tetrazole ring acts by inhibiting

vitamin K epoxide reductase enzyme which reduces vitamin K. The net result is decreased prothrombine level.

Quinolones

Mainly due to their relative safety and good potency, quinolones have gained popularity in clinical practice. The addition of fluoride even increased their potency. They are bactericidal agents as they act by inhibition of topoisomerase II (DNA gyrase) and IV enzymes. These enzymes are responsible of changing the DNA shape, but not structure, during its replication. Inhibiting these enzymes would interfere with DNA synthesis. By means of macrophages and other inflammatory cells, fluoroquinolones possess good tissue distribution and are able to reach bone and sites of inflammation.

Quinolones have good oral absorption, although should not be taken with antacids, calcium and other ions as this may interfere with its absorption.

Second generation fluoroquinolones (**ciprofloxacin** and **norfloxacin**) act mainly on gram-negative and some gram-positive bacteria, while the agents of the 3rd generation (**levofloxacillin**) have extended functions on the gram-positive species. The newly developed fourth generation (**moxifloxacillin**) has even more action on both gram-negative and gram-positive with some actions on anaerobes. Table 3.4 list common fluoroquinolones and their doses.

Resistance to these agents by pseudomonas and some *staphylococci* was reported. These strains may alter their DNA enzymes or cell permeability, rendering these agents ineffective.

Adverse effects to quinolones include GIT troubles (nausea, vomiting and diarrhea), central nervous system symptoms (headache, drowsiness, and insomnia) and connective tissue effects. Quinolones should be avoided in epileptic patients. The effects on articular cartilage, tendons and other connective tissues were only proven on experimental animals, but as a precaution, it should be avoided in children and elderly. It also increases muscle weakness, an effect which contraindicates their use in patients with Myasthenia

Table 3.4: Members of fluoroquinolones, route of administration and dosage

Second Generation		
Ciprofloxacin	Oral	500 mg/bid
Ciprobay		
Cipromax		
Ciprofar		
Ofloxacin	Oral	200 mg/bid
Tarivan 200		
Ofloxin 200		
Oflicin 200		
Third Generation		
Levofloxacin	Oral, IV	500 mg/oid
Levoxin		
Lee-flox		
Fourth Generation		
Moxifloxacin	IM, IV	400 mg/oid
Avalox 400		
Idelox 400		
Moxacin 400		

gravis. Other adverse reactions include phototoxicity and allergy. Phototoxicity may necessitate the use of sunscreen if exposure to the sun is mandatory.

Nitroimidazoles

Nitroimidazoles are basically antiprotozoal agents used commonly to treat amoebic infections. Their effect on anaerobic gram-negative bacteria is the reason behind its popularity. It is the agent of choice to treat pseudomembranous colitis, a resultant superinfection due to the use of a broad-spectrum antibiotic. In dentistry, it is commonly used to treat anaerobic infections caused by black pigmented bacteria, formerly known as bacteroides, as ANUG and aggressive periodontitis. They are also used in colon preparation before surgeries as it has anti-inflammatory properties in the large intestine. Nitroimidazoles are effective antidiarrheal agents.

Nitroimidazoles act by binding to macromolecules, including DNA, causing their dysfunction and toxicity. They are bactericidal and have good tissue distribution.

Strains of lactobacillus, *A. israelii*, *P. denticola*, *E. corrodens* and *A.a* were reported to be resistant to metronidazole. Such resistance is mainly due to enzyme deactivation, decreased cellular concentration or even by intrinsic resistance mechanism.

Being metabolized in the liver, metronidazole is affected by the concurrent use of liver enzyme inducers or inhibitors and precautions should be undertaken accordingly (see the interaction box).

Common side effects of these agents include metallic taste (due to its re-absorption into the enterohepatic circulation), GIT troubles, headache, and peripheral neuropathy. It is associated with the characteristic disulfiram reaction or antiabuse effect if taken with alcohol, so it should not be combined with it. It was also reported that nitroimidazoles are potentially mutagenic, so should be avoided in pregnancy. Agents and doses of nitroimidazoles are listed in Table 3.5.

Macrolides

Literally, a macrolide means a large molecule. Naturally, they are derived from *Streptomyces erythreus*, and the oldest agent is erythromycin. Erythromycin is considered as an alternative to β-lactam agents when they are contraindicated.

Table 3.5: Members of nitroimidazoles, route of administration and dosage

Member	*Route*	*Dosage*
Metronidazole **Flagyl** **Amirzole** **Metronal**	Oral, IV	250–500 mg/tid
Tinidazole **Protozol**	Oral	250–500 mg/tid

They are bacteriostatic, acting by binding to the 50S ribosomal subunit and, hence, block protein synthesis by the bacterial cells. In high doses, erythromycin is bactericidal. Macrolides have good tissue distribution and are able to reach the sites of inflammation via the inflammatory cells.

Erythromycin has a similar spectrum to penicillins, being active mainly on gram-positive bacteria. However, erythromycin is inactivated by gastric acid and has poor lipopolysaccharide penetration. This means that it may have poor effects on gram-negative bacteria. In a way to protect erythromycin from gastric acid, they are either present with enteric coating or in easterified form. Newer members like clarithromycin and azithromycin have been developed to overcome such disadvantages (Table 3.6).

Clarithromycin is a methylated form of erythromycin, causes less GIT upset, and enhances patient compliance as it is used twice daily. It acts on gram-positive as well as gram-negative and anaerobes (*P. gingivalis* and *A.a*). It is also excreted in saliva in high concentrations.

Azithromycin adds more compliance as it is used once per day. However, it has lesser activity on gram-positive bacteria when compared to erythromycin.

Telithromycin, a ketolide, was developed to act on resistant strains (methylase-producing) and possesses activity like that of azithromycin.

Table 3.6: Members of macrolides, route of administration and dosage

Member	*Route*	*Dosage*
Erythromycin **Erythrocin 500** **Erythrin 500**	Oral	250–500 mg/ qid
Clarithromycin **Claribiotic** **Clarithro**	Oral	250–500 mg /bid
Azithromycin **Azithrolid** **Zithromax**	Oral	250–500 mg /oid

Macrolides are metabolized in the liver and excreted in bile. They are liver enzyme inhibitors, with consequent inhibition of other drug metabolism if taken at the same tame (see the drug interaction box).

Common adverse reactions to macrolides include GIT problems, ototoxicity and cholestatic jaundice, especially with the estolate form. Their use may precipitate acute attacks of porphyria (with sensory and motor neuropathy), so their use is contraindicated in those patients. Their use is also associated with altered taste, due to altered salivary composition.

Lincomycins

Naturally produced from *Streptomyces lincolnensis*, lincomycins' structure may be modified by the addition of chlorine to produce the more commonly used clindamycin. Due to its good distribution in bone and the ability to act on gram-negative bacteria, clindamycin has gained its popularity for the treatment of odontogenic infections. Clindamycin gets concentrated in inflammatory cells and hence, reaches sites of inflammation at high concentrations. It acts mainly on gram-negative anaerobic bacteria. It is bacteriostatic as it acts on the bacterial ribsosomal 50S subunit, thus, interfering with protein synthesis. It is metabolized in the liver, so precautions should be taken when used in patients with liver disease. Members and doses are listed in Table 3.7.

One of the common adverse reactions to the use of clindamycin is **pseudomembranous colitis**, although it might be also caused by the use of other broad spectrum antibiotics, like cephalosporins. *Clostridium difficile* is one of the normal flora of the intestine. It is a

Table 3.7: Members of lincomycins, route of administration and dosage

Member	*Route*	*Dosage*
Clindamycin **Dalacin-C** **Clindam 300**	Oral, IV, IM	300 mg/tid

gram-positive spore forming bacillus which is resistant to clindamycin. It may proliferate when the other members of the bacterial flora are suppressed by the used antibiotic. Once established, the infection is associated with watery bloody diarrhea along with necrosis, microabscesses and pseudomembrane formation. The infection is treated by metronidazole. However, severe cases would require the use of vancomycin.

Tetracyclines

Tetracyclines, as the name implies, are cyclic structures composed of four fused rings. They are naturally produced from *Streptomyces*.

They are bacteriostatic in action, acting by inhibiting protein synthesis by binding to the 30S subunit. They are broad spectrum, acting on both gram-positive and negative bacteria. In addition, non-bacterial microorganisms can be affected. *A.a* and other periodontopathogens are susceptible to tetracycline, so it may be chosen to treat aggressive periodontitis or refractory periodontal diseases. It also possesses non-bacterial properties like anticollagenase activity, substantivity and enhancement of reattachment and regeneration of periodontal tissues.

Resistant strains to tetracycline include α-hemolytic *Streptococcus* (*S. mitis*) and some anaerobes (*P. gingivalis, P. intermedia and Bacteroids forsythus*). These bacteria are able to avoid intracellular concentration by diminishing membrane permeability, enhancing drug efflux, or both. Others are able to produce ribosomal protecting proteins to destroy or inactivate the agent.

Their use should be avoided with the intake of diary products, antacids or other ions like iron or magnesium, as this may lead to the formation of non-absorbable chelates. Tetracyclines get concentrated at liver, kidneys and calcifying tissues, including neoplasms. They also achieve high salivary concentrations, so local action can be anticipated. Metabolism is by means of the liver, and they are excreted in bile where re-absorption into the enterohepatic circulation may occur. The members of tetracyclines are presented in Table 3.8.

Table 3.8: Members of tetracyclines, route of administration and dosage

Member	*Route*	*Dosage*
Tetracycline	Oral	500 mg/tid
Tetracid		
Hostacycline		
Oxytetracyline	Oral	500 mg/bid
Oxytetracid		
Doxycycline	Oral	100 mg/bid
Doxymcin 100		
Farcodoxin 100		
Minocycline	Oral	100 mg/oid

Common adverse effects to tetracyclines include GIT irritation, especially if taken with diary products. The problem may be aggravated by the use of antacids. Doxycycline and minocycline have more patient compliance as their use is less frequent per day. Their use is also associated with lesser ionic chelation and other side effects. Photosensitivity may lead to sun burn or skin rash, so the patient should be warned about such effects. In patients with lupus erythematosus, however, tetracycline use is contraindicated. Symptoms associated with vestibular changes as dizziness, vertigo and tinnitus are possible as the drug is concentrated in the endolymph of the ear. Superinfections, as with other broad-spectrum antibiotics, may also occur with the use of tetracyclines. Because they bind and concentrate in calcified tissues, tetracyclines should be avoided in pregnancy, breastfeeding and children under the age of six years. Otherwise, permanent staining and hypoplasia of teeth and disturbed bone growth may occur. Fetal hepatotoxicity is also possible if used in pregnancy.

Aminoglycosides

Structurally, aminoglycosides are composed of two amino sugars linked by a glycosidic bond. Naturally, they are produced either from *Streptomyces* (those ending with the suffix _mycin) or *Micromonospora* (those ending with _micin). Agents of this group

are listed in Table 3.9. As their use is associated with serious toxicities, they are reserved for severe infections, like those caused by gram-negative aerobic bacilli. So, safer agents should be tried first. They also have a synergistic action if combined with β-lactam antibiotics. In this case, the β-lactam agents serve by disturbing the cell wall allowing more aminoglycosides to enter the bacteria.

Aminoglycosides act on gram-negative aerobic, facultative anaerobic but not strict anaerobic. Their entry is based on the presence of oxygen transport system and the lesser oxygen requirement of the cell, the lesser its concentration intracellularly. They also need what is called membrane pores for entry, a structure present only in gram-negative membranes. Therefore, resistant bacteria would be those strict anaerobic, as well as those able to reduce their oxygen uptake. Some strains block the porin channels while others produce acetyl transferrase inactivating enzymes. Once inside the cell, they bind to the 30S protein, thus, inhibiting protein synthesis. They also act by interrupting mRNA reading producing defective, non-functional or even toxic proteins. Although act by inhibiting protein synthesis, aminoglycosides are bactriocidal by a process which is still unknown.

Table 3.9: Members of aminoglycosides, route of administration and dosage

Member	*Route*	*Dosage*
Streptomycin	IM	1g/oid
Streptomycin		
Gentamycin	IM, IV	80 mg/tid
Garamycin 80		
Refobacin 80		
Tobramycin	IM, IV	80 mg/bid
Tobracin		
Nebcin		
Amikacin	IM, IV	100 mg /bid
Amikin 100		
Amikacin 100		

Due to the polycationic structure, these agents have poor oral absorption, so, given by the parenteral route. Neomycin is highly toxic to the kidneys and only is present in the topical or oral form (for local treatment of the bowel). Aminoglycosides concentrate mainly in the endolymph and perilymph of the ear and the renal cortex, the reason behind their ototoxicity and nephrotoxicity. In addition, they are not metabolized in the body; instead, they are excreted in the active form by the kidneys.

Common adverse reactions to aminoglycosides include ototoxicity. It is the result of destruction of hair cells in the organ of Corti, which is irreversible. The patient may complain of deafness and vertigo (loss of balance), the latter is due to the effect on the vestibular apparatus. Reversible, and sometimes, irreversible damage to the kidneys is also possible as these drugs concentrate in the renal cortex. Topically applied agents may be associated with allergic reactions, seen as contact dermatitis.

Vancomycin

Vancomycin, a glycopeptide, is used parentally for severe infections as septicemia, severe bone infections, and infections with resistant strains as MRSA or MRSE. It is also used to treat pseudomembranous colitis when metronidazole treatment fails. They are also used for prophylaxis against infections. It is administered by slow IV infusion over 60 to 90 minutes (Table 3.10). No oral administration is possible, except, for local treatment of the intestines as in *C. difficile* infections. It is partially metabolized and excreted by the renal system.

Table 3.10: Members of vancomycin, route of administration and dosage

Member	*Route*	*Dosage*
Vancomycin **Vancocin 500** **Vancolon 500**	Slow IV infusion	500 mg

Vancomycin is bactriocidal, acting by the inhibition of peptidoglycan polymerization. It also acts by damaging the cell membrane underneath by interrupting its phospholipids. Its action is exerted mainly on gram-positive strains including the multidrug resistant *Staphylococcus aureus* and epidermidis (MRSA and MRSE). Resistance to vancomycin may be the result of altered permeability to the drug with or without decreased binding to its receptor.

Common adverse reactions include fever, chills and thrombophlebitis at the venous access site. Rapid IV infusion produces "red man syndrome", characterized by flushing and shock. Such effect is produced by the release of histamine and once occurred, it can be managed by the administration of antihistamine and corticosteroids. Pretreatment with antihistamine may be provided as a preventive measure. Other adverse reactions include ototoxicity and nephrotoxicity, especially if co-administered with aminoglycosides.

CLINICAL USE OF SYSTEMIC ANTIBIOTICS

In the following section, the main uses of antibiotics in dentistry will be discussed. Some conditions requiring antibiotic treatment will be briefly presented, as regard to the causative microorganism and the most effective antibiotic to use. Box 3.3 lists the main dental uses of systemic antibiotics. Table 3.11, provides a summary of the common antibiotics along with their spectra.

Management of Established Infections

Although antibiotics only assist the body immunity, they are needed in the management of odontogenic infections. However, not all infections need antibiotic therapy and the clinician should focus

Box 3.3: Clinical use of antibiotics
• Treatment of established infections
• Adjuvant in the management of periodontal diseases
• Prophylaxis against surgical wound infections (SWI)
• Prophylaxis against blood borne "metastatic" infections

Table 3.11: Summery of the spectrum of each group of antibiotics

Agent	*Range of activity*
Penicillins	
Penicillins G/V	Mainly Gm (+)ive with some Gm –ive
Amoxicillin	Gm –ive but lesser gm (+)ive than penicillin
Cloxacillin	Active on penicillin–resistant staph
Cephalosporins	
1st generation	Gm (+)ive and gm –ive
2nd, 3rd and 4th generation	More activity to gm –ive. 4th generation act especially on strains resistant to 2nd and 3rd generations
Macrolides	
Erythromycin	Gm +ive, like penicillin
Clarithromycin	Gm +ive and gm –ive
Azithromycin	More activity to gm –ive, less active on gm +ive than erythromycin
Telithromycin	Like azithromycin, but more active on resistant strains
Fluoroquinolones	
Ciprofloxacin	Gm –ive and some gm + ive
Levofloxacillin	Gm –ive with more activity on gm +ive
Moxifloxacillin	Gm –ive, gm + ive and anaerobes
Metronidazole	Antiprotozoal with effect on gm –ive anaerobic bacteria
Clinamycin	Anaerobic with some gm +ive stains
Tetracyclines	Gm +ive and gm –ive
Aminoglycosides	Gm –ive/aerobes
Vancomycin	Gm +ive, mainly MRSA/MRSE and *C. difficile*

on removal of the cause. Removal of the cause is translated in clinical terms into drainage (by RCT, extraction, or I and D), debridement, cleansing and dressing. These surgical procedures are usually enough as the area of head and neck is rich in blood supply, which is further enhanced by drainage. Usually, the body is able to reverse the condition towards healing without the use of antibiotics.

Moreover, if antibiotics are used alone, the irritating focus of infection will not be totally removed and relapse will occur. Their administration in that case will be like adding risks and burden on the body. The clinician should be careful whenever he prescribes an antibiotic, regarding its risks and benefits. They should be provided only when their benefits outweigh risks. If the infection is accompanied with systemic manifestations as fever >100° F or 38.3 to 38.8° C, malaise, lymphadenopathy or trismus, antibiotic treatment is usually indicated. Infection is also associated with elevated blood pressure, high pulse rate (100 bpm), and rapid respiration (>20/min). Severe conditions should be referred to a specialist and hospital care may be necessary. These include conditions with breathing or swallowing difficulties, high grade fever (> 102° F), pulse > 100 bpm, or severe trismus with mouth opening less than 10 mm.

Certain odontogenic infections are known to usually have the systemic manifestations previously described. So, they most probably require antibiotic treatment along with the surgical part. Box 3.4 lists the common odontogenic infections indicating use of antibiotics and Box 3.5 lists those which do not. Generally, an empirical antibiotic is used on a presumptive basis according to the knowledge of the causative organism and the antibiotic spectrum. Of course, the best method is to have culture and sensitivity tests to provide the best matching antibiotic and prevent unnecessary overdose or wrong antibiotic. This procedure is known to take time, and for convenience, it is performed in persistent infections, recurrent conditions, dangerous or rapidly spreading diseases, and in case of compromised host defense. The empirical use of antibiotic is started and maintained until the results from the lab show.

Acute pericoronitis, inflammation of the pericoronal flap (operculum), is usually associated with a partially erupted tooth. The etiologic cycle begins once inflamed as food entrapment and trauma from opposing dentition aggravate the condition. In moderate to severe conditions the following symptoms are present: fever, malaise lymphadenopathy, and trismus. Advanced conditions

Box 3.4: Established infections in relation to oral and facial tissues

Acute Periodontal Conditions
- Acute pericoronitis (moderate-severe)
- Necrotizing periodontal conditions
- Disseminating periodontal abscess
- Specific bacterial infections:
  - *N. gonorrhoeae*
  - *S. gingivostomatitis*

Acute Periapical Conditions
- Acute apical abscess
- Acute exacerbation of chronic abscess (phoenix)

Major Infections of Bone and Face
- Cancrum oris "noma"
- Fascial space infections "cellulitis"
- Osteomyelitis
- Osteoradionecrosis
- Actinomycosis

Salivary Gland Infections
- Bacterial sialadenitis

Trauma Related Conditions
- Extensive laceration
- Visibly contaminated wounds
- Delayed wound management
- Contaminated open fractures

Other Infections of Oral Relevance
- Tuberculosis
- Leprosy
- Syphilis
- Scarlet fever "scarletina"

Box 3.5: Infections not requiring antibiotic use

- Chronic gingivitis
- Mild-moderate pericoronitis
- Non-disseminating periodontal abscess
- Chronic draining abscess
- As a complement in RCT
- Dry socket

are associated with pericoronal abscess which may spread to adjacent facial spaces. The associated microorganisms include *Borrelia vincentii* and *Fusiformis dentium*. The condition is best treated with **amoxicillin** with **metronidazole** and a **mouthwash**. However, the condition needs debridement with drainage (by anteroposterior incision) in case of abscess in fluctuant stage. Further treatment considerations include operculectomy or extraction for definite treatment of the case. Acute pericoronitis may be accompanied with ANUG.

ANUG is usually caused by several factors, most important of which is the underlying systemic condition. Usually, stress, malnutrition, smoking or debilitating diseases are present. Clinically, ANUG is associated with acute inflammation, necrosis and ulcerations. The infection is described as a fusospirocheal one with an invasive component, a factor important to be considered during its management. The usual sings and symptoms include fever, GIT troubles, fetid odor and increased salivation. The condition is initially treated by debridement (with hydrogen peroxide swap under topical anesthesia), supragingival scaling and medications. The following antibiotics have been frequently used: **amoxicillin** or **macrolides** with **metronidazole**. The condition needs several recall visits and the underlying local and systemic factors should be corrected. The condition may be mistaken with several other conditions as streptococcal gingivostomatitis, gonococcal gingivitis, diphtheria, or acute herpetic gingivostomatitis.

Streptococcal gingivostomatitis is a gram-positive coccal infection caused by *S. viridans* advancing from inflamed tonsils. The condition is not associated with linear erythema as in ANUG. Instead the gingiva is diffusely inflamed. In addition, neither necrosis nor fetid odors are present. The condition is managed by **amoxicillin** or **erythromycin**.

Gonococcal gonorrhea is a gram-negative infection caused by *Neisseria gonorrhoeae*, and is one of the sexually transmitted diseases. It is associated with sore throat and suppurative inflammation

with pseudomembrane slough and ulcers. The condition is treated by amoxicillin, ciprofloxacin or cephalosporins.

Diphtheria, caused by the gram-positive *Corynebacterium diphtheriae*, is characterized by sore throat with tonsillar lesions and pseudomembrane which is difficult to wipe off. Fever, malaise and lymph node enlargement may also be present. The condition may get complicated by mycocarditis or paralysis. It is treated by antibiotics (penicillins or erythromycin) and antitoxins.

ANUG may progress to involve the investing bone causing **NUP**. It may involve other facial tissues causing more serious condition known as **cancrum oris** or **noma**. The disease involves a necrotizing and gangrenous process causing a cone-shaped lesion with the apex directed superficially. The condition needs antibiotic treatment with amoxicillin or aminoglycosides combined with metronidazole. Supportive treatment and local debridement are of great importance.

Severe **periodontal abscess** may be associated with throbbing radiating pain and systemic manifestations. Drainage, either intrasulcularly or by external I and D, is necessary. The condition should be differentiated from acute apical abscess as the nonvital tooth will require drainage through RCT.

Acute apical periodontitis (AAP) is moderate to severe inflammation of the apical periodontal ligament and it is associated with severe pain. It may result from mechanical, chemical or biologic insults introduced to that tissue either by improper RCT or by the caries process. Analgesics, antibiotics and drainage along with occlusal relief are needed. The condition may be converted to **acute apical abscess** (AAA), which is also a painful condition. The condition is associated with swelling and expansion which is more apically located when compared to lateral periodontal abscess. The involved tooth is nonvital or with large caries/metallic restorations. It needs drainage, either through RCT or by extraction, antibiotics and analgesics. The chosen agents include amoxicillin or penicillin (but not augmentin, as it was found to be of no more benefit).

Metronidazole may be added to cover the anaerobic species. Clarithromycin (but not erythromycin as it is less effective on anaerobes and gram-negative) or clindamycin can be used as substitutes. AAA may be superimposed on chronic apical one, a condition known as **recrudescent abscess**. The condition may be caused by blockage of the spontaneous drainage provided by the formed fistula. Its clinical presentation is similar to AAA and requires the same treatment. AAA may also spread into tissue spaces causing fascial space infections.

Fascial space infections are spreading in nature with inflammatory edema and microorganisms entrapped in the tissue spaces. Pain, swelling, fever, malaise, and lymph node abnormality are usual. Usually, *penicillin* (with *cloxacillin* for resistant Staph.), or *clarithromycin* are used. A serious complication as a result of spreading of facial cellulitis is Ludwig's angina. It is a bilateral involvement of submental, sublingual and submandibular spaces with board-like brawny swelling. It may be related to infection spread from the 2nd or 3rd molars. Difficulty in breathing, swallowing or both may necessitate hospital care. Its treatment follows the same general principles of drainage and antibiotics, however. Another serious sequel of infection spread in the fascial spaces is the cavernous sinus thrombosis which may lead to blindness or even death. In such a case, antibiotics, anticoagulants, and surgical drainage are the required treatment. Antibiotics should be administered to prevent such dangerous conditions.

Osteomyelitis, inflammation of bone marrow and endosteum/periosteum compartments, may require prolonged antibiotic treatment, ranging from four to eight weeks for the acute type, while reaching up to six months in the chronic one. The responsible microorganisms include *Peptostreptococcus* and other anaerobic gram-negative species. The chosen type of antibiotic is usually clindamycin, owing to its ability to concentrate in bone. Other antibiotics used include ciprofloxacin and cephalosporins. Management is by surgical debridement (to remove infected plate, wire or teeth) sequestrectomy, hyperbaric oxygen therapy, treatment

of the underlying systemic factors (nutrition, immune suppression, debilitating diseases).

In cases of irradiated jaws, **osteoradionecrosis** is one of the complications that requires months, if not years, in order to heal. Osteoradionecrosis is a hypoxic nonhealing lesion that may occur in bones exposed to high doses of radiotherapy (6500 rad or 65Gy). The lesion itself is not an infection and the use of antibiotics is either to prevent or treat secondary bacterial infections. Once established, the formed sequestration should be removed, antibiotic should be administered and considerations about hyperbaric oxygen therapy should be made. Such patients may require antibiotic administration as prophylaxis to prevent infections in case of extraction, implant placement or RCT.

Actinomycosis is a soft tissue infection which tends to localize in the form of pseudotumor in area close to the neck. It is dusky-red in color and has multiple sinus tracts. The causative microorganisms include *Actinomyces israelii* and *A. viscosus* (anaerobic gram-positive). The infection is quite stubborn requiring long time to heal. The used antibiotics include: penicillin (IV), amoxicillin, tetracycline or erythromycin. In addition, I and D and excision of the sinus tracts should be done.

Bacterial sialadenitis is an infection of the major salivary glands. It is usually mixed in nature with pain, erythema, and suppuration. Its incidence is associated with poor nutrition, dehydration or chronic illness, all of which can be present in elderly. *Staphylococuss aureus* is associated with the infection. The infection needs antibiotic treatment and the following are commonly used: penicillin, amoxicillin or 1st generation cephalosporin. Culture and sensitivity tests may be required, however.

Trauma-related infections that need antibiotic treatment include extensive lacerations, contaminated wounds and delayed wound management (> 3 h). **Extensive lacerations** will also require multilayered suturing in addition to the antibiotic regimen. **Contaminated wounds** would also need hemostasis, cleansing, debridement and closure. The usual antibiotic prescribed is

penicillin. In case of **tooth avulsion**, antibiotics are provided to guard against any possible infections as the re-implanted tooth is considered infected. Other treatment considerations include tetanus boost or vaccine, splinting, recall visits and RCT. Contaminated open fractures or delayed management of clean open fractures, too, are assumed to be infected and require antibiotic treatment. **Open** or **severe fractures** are at high liability to get infected and, hence, the use of antibiotics is justified.

Scarlet fever is a gram-positive streptococcal infection of the pharynx. Fever, vomiting and lymphadenopathy are usually present. The tongue presents characteristic lesion during the early and late phases of the infection. Early lesion is characterized by prominent erythemic papilla over a white coat producing a "strawberry" appearance. The late lesion is devoid of the white coat, hence, resembles "raspberry". The lesion is treatable with penicillin, cephalosporin or erythromycin.

Tuberculosis is anaerobic infection with the acid fast bacillus *Mycobacterium tuberculosis*. It is related to the oral cavity as it may be manifested in the form of ulcers which have characteristic punched out appearance with everted edges. Scrofula, which is massive cervical lymph node enlargement with discharging sinus, may be seen too. The case would require consultation and treatment by a specialist.

Syphilis, a spirocheatal infection with the gram-negative *Treponema pallidium*, manifests itself in the oral cavity as ulcers through its three stages. Accordingly, chancre, snail tract ulcers, or deep punched out ulceration may be present. The condition should be referred to the specialist of interest for treatment.

Leprosy, an infection caused by *Mycobacterium leprae*, causes oral and cutaneous hypopigmented lesions as well as, loss of sensory functions. This condition, too, should be referred to a specialist.

Adjuvant in the Treatment of Periodontal Diseases

Certain forms of periodontitis may require the use of suitable antibiotics along with the conventional periodontal therapy and oral hygiene measures. Scaling and root planning should be done

first and the patient cooperation should be assured. Some forms of periodontitis show no response to the provided conventional therapy and these are: Refractory periodontitis, aggressive periodontitis and periodontitis as a manifestation of systemic disease (Box 3.6). The use of antibiotics, either systemically or locally, aids the conventional therapy by providing a means of accessibility to deeper sites.

Refractory periodontitis is defined as continuous loss of clinical attachment despite instrumentation and good oral hygiene under healthy endodontic conditions. The condition may be associated with deep invasions by the causative microorganisms, defective host defense, or both. Culture and sensitivity tests may be needed to identify the causative organisms and the most matching antibiotic against them. The following antibiotics may be useful: Augmentin, clindamycin, tetracycline, ciprofloxacin, azithromycin and metronidazole. Sometimes, it might be necessary to combine two antibiotics together in order to increase the spectrum and to lower the individual doses. This usually means the addition of metronidazole to another agent. Such therapy may eliminate the need for surgical periodontal therapy.

Aggressive periodontitis have characteristic clinical features of rapid bone loss in relatively young individuals. The radiographic appearance of angular arch-like defects localized to the molar/incisor (LAP) area is noticeable. The associated microorganisms include *A.a* and *P. gingivalis*, which are virulent and invasive. A possible defective immunity, as well as, cementopathy may be also present. The condition may respond to conventional therapy, modified Widman flap and tetracycline given at the dose of

Box 3.6: Periodontal conditions requiring antibiotic administration
Refractory periodontitis (RP)
Aggressive periodontitis (AP)
Periodontitis as manifestation of systemic disease
Implant associated infections (peri-implantitis)

1 g/day in divided dose for two weeks. Recall visits should be made every month and good oral hygiene should be optimized. Another antibiotic regimen includes the combination of amoxicillin and metronidazole. The generalized form may be treated as refractory periodontitis.

Periodontitis as manifestation of systemic disease is associated with lowered immune response which may be associated with hematological, as leukemia and leukopenia, or genetic diseases, as Down syndrome. It is differentiated from aggressive periodontitis in that the medical problem is a major factor in the disease process, while in AP, it is not. The medical evaluation is mandatory. The conventional therapy may be augmented by the use of antibiotics according to the results of culture and sensitivity tests, however.

In **implant-associated infections** or peri-implantitis, bone loss and inflammation may lead to implant failure. Antibiotics are administered (for 10 days) as a nonsurgical solution which may spare the patient from additional surgeries. In this case, it is clear than the benefits of antibiotics outweigh their risks. Conventional therapy and good oral hygiene are mandatory.

Prophylaxis against Surgical Wound Infections (SWI)

Some surgeries, especially major ones, are at high susceptibility to get infected even when strict aseptic principles are adhered to. In addition, contamination may be present in some injuries. Antibiotics are provided to prevent the establishment of the infection which delays healing and needs higher doses and longer periods of antibiotic therapy. Prophylaxis, when indicated, uses shorter time and lower dose of antibiotics than that used to manage established infections. This means lesser chances of developing bacterial resistance, lesser burden on the body and better healing potential. So, prevention of SWI would help both the patient and the dentist. The procedure must be as aseptic as possible, though. Those conditions at low risks of infections should not receive antibiotics as their use is not justified, except in those with defective immunity.

The conditions at higher risks are described in the following sections and are listed in Table 3.12.

Table 3.12: Surgical wound prophylaxis, the recommended conditions vs. low risk cases

Cases requiring antibiotic prophylaxis	*Cases not requiring antibiotic prophylaxis*
Class of surgery	
• Major oral surgery class I, extraoral surgery when duration > 2 h • Combined intraoral/extraoral approach (II surgeries) • Major oral surgeries involving the manipulation of infected tissues (III and IV surgeries)	• Minor oral surgeries (frenectomy, minor alveoplasty, biopsy, small bone lesions) • Major class I surgery < 2 h duration
Trauma-related cases	
• Extensive lacerations • Closed fractures if managed by intraoral approach, or when the duration > 2 h • Open fractures, even when first seen	• First seen lacerations < 3 h • Small, clean lacerations • Closed fractures managed by extraoral approach within 2 h
Cases irrespective of class of surgery or duration	
• Patient with ASA* > 2 • Patient with poor immunity • Preoperative stay > 3 days • Placement of implant • Placement of grafts	

* ASA is the classification of American Society of Anesthesiologists and is indicated as follows: ASA 1 = healthy, no medical problems, ASA2 = mild systemic disease which is well controlled, ASA3 = severe systemic disease or controlled disease of more than one system which is not incapacitating but with some functional limitations, ASA4 = severe systemic disease which is a constant threat to life (or an end-stage disease), ASA5 = morbid, not expected to live for 24 h without an operation, ASA6 = declared brain-dead patient.

Regarding the **class of surgery** (Table 3.13), major oral surgeries, either intraoral or combined intraoral/extraoral (class II), even if kept clean, will need antibiotic prophylaxis. It is difficult to attain aseptic field in the intraoral environment when compared to that of skin. Extraoral surgeries (Class I) do not need antibiotic prophylaxis as they are clean in nature. However, class I surgeries are prone to infections when the procedure takes more than two hours. Minor oral surgeries, like extraction, frenectomy, minor alveoplasty, are at lower risk of infections and, hence, no antibiotic is required. Surgeries that involve the manipulation of contaminated tissues are associated with major break through in the aseptic technique. Antibiotics should be provided as the risk of infection is high.

Traumatic injuries of the soft tissues may require prophylaxis if they exhibit **extensive laceration** or when they are **visibility contaminated**, even if first seen. Small, noncontaminated and first seen lacerations are at lower risks of developing an infection. However, if management is delayed more than three hours, the bacterial population increases to a level that these injuries are considered infected. **Open fractures** of the facial bones also need prophylaxis as they are at high risk of infection. Antibiotics should be provided immediately and maintained till get managed. If the

Table 3.13: Classes of oral and maxillofacial surgeries

Minor surgeries	Simple surgeries, e.g. impactions, alveoloplasty
Class I	Clean surgery (at skin), in clean aseptic field, e.g. TMJ, parotid gland surgeries
Class II	Clean-contaminated, combined intra- and extra-oral approach, or visibly contaminated, e.g. major tumor surgery, major preprosthetic surgery
Class III	Contaminated surgery, acute inflammation, or with major breakthrough the aseptic technique, e.g. compound fractures
Class IV	Dirty, infected (with pus) surgery, e.g. visibly contaminated wounds

management is delayed for more than three hours without the use of antibiotics, the wound is considered infected. **Closed fractures**, on the other hand, require prophylaxis, if to be managed by intraoral approach or when the procedure itself requires more than two hours. Otherwise, first seen closed fractures managed extra orally and within two hours do not require prophylaxis.

Some conditions may require antibiotic prophylaxis even when the condition or the surgery does not indicate so. Patients with debilitated immunity either by a systemic disease or local factors (as radiotherapy) are at higher risks to develop infections and will need more time and more aggressive therapy to treat established ones.

Generally speaking, patients with ASA > 2 require antibiotic prophylaxis to prevent life-threatening infections (Table 3.12). **Implants** and **bone grafts** induce local changes that the host defense mechanism is altered. Both procedures are invasive in nature, expensive and time consuming. Antibiotic prophylaxis is considered a safe and cheap option when compared to the possible infection.

The most commonly involved **microorganisms**, regarding orofacial surgeries, include aerobic gram-positive *Streptococcus*, anaerobic gram-positive *Peptostreptococcus* and rods. It appears that the aerobic stains should be primarily covered, while anaerobic ones do not need complete coverage. Accordingly, *penicillins*, but not *amoxicillin* or *ampicillin*, *erythromycin* and *vancomycin* are good choices. First generation cephalosporins also provide good results, while other generations focus more on the gram-negative species. In case of extraoral surgeries, cloxacillin is added to penicillin in order to cover the resistant *Staphylococcus aureus* strains. Vancomycin is especially active on those strains, as well as, on *Streptococcus*.

Oral route of administration is an acceptable and less invasive one. It is used in surgeries in which local anesthesia was used. Oral administration should start one to two hours before the surgery. Parenteral route (slow IV injection or continuous infusion) is used in case of general anesthesia, high-risk patients, and in those unable to take anything by the mouth. In these patients, antibiotics should be started at the time of induction. Although double the therapeutic dose, prophylactic antibiotics are provided in single doses. The

duration at which intraoperative doses are provided is half that of the therapeutic one (Table 3.14). No postoperative doses are required.

Prophylaxis against Metastatic Infections

Metastatic infections are defined as infections developing at distant or anatomically separate locations of their original site. Microorganisms gain entry through oral tissues to infect the heart or artificial joints. For a metastatic infection to occur, three factors should be concurrently present: (1) susceptible tissue (valvular defect), (2) microbial seeding mechanism (surgery or bleeding); and (3) impaired host defense. The most dental procedures associated with significant bacteremia as well as those which can be done without risk of developing an infection are listed in Box 3.7.

Prophylaxis against Bacterial Endocarditis

Bacterial endocarditis is the infection and inflammation of the endocardium or heart valves which are usually defective. The defect may be produced by turbulent blood flow which causes loss of endocardium and exposure of the collagen layer which gets covered

Table 3.14: Antibiotics commonly used in prophylaxis of SWI, route, dose and duration. Comparative therapeutic doses and duration are also present for comparison

Agent	*Route*	*Therapeutic dose*	*First prophylactic dose*	*Intra-operative dose*
Penicillin G	IV	1 mega unit/6 h	2 mega units	Every 3 h
Penicillin V	Oral	500 mg/6 h	1 gram	
Cloxacillin	Oral/IV	500/6 h	1 g	2–3 h
Cephalosporins (Cefadroxil)		500/6 h	1 g	3 h
Clindamycin	Oral/IV	300 mg/6 h	600 mg	3 h
Erythromycin	Oral	400 mg/12 h	800 mg	6 h
Vancomycin	IV	500 mg/6 h	1 g	3 h

Box 3.7: Dental procedures that need antibiotic prophylaxis and those that do not

Prophylaxis needed

- Dental extraction
- Implant surgeries
- Root canal treatment beyond the apex
- Endodontic surgeries
- Periodontal procedures (scaling, root planing, surgeries, probing)
- Subgingival placement of fibers, strips, and regeneration devices
- Local anesthesia (intraligamental)
- Prophylaxis cleaning involving bleeding
- Initial placement of orthodontic bands

Prophylaxis not needed

- Restorative procedures, with or without gingival retraction cords
- Nonintraligamental local anesthesia
- Root canal treatment
- Post and core placement
- Postsurgical suture removal
- Taking impressions
- Placement of orthodontic appliances
- Shedding of primary teeth
- Topical fluoride application

by fibrin, platelets and RBCs. A seeding mechanism (bacteremia producing surgery or action) causes the infection of the preformed vegetation or the initiation of a new one. The most commonly associated microorganisms include the *α-hemolytic Streptococcus*, which is an oral bacterium able to produce polysaccharides, the sticky component of dental plaque. This layer acts by entrapping additional fibrins, platelets and RBCs into the septic vegetation. This vegetation acts as a reservoir for the pathogenic bacteria and as impedance to the blood flow which compromises the heart functions.

On detachment, septic embolism may occur. Other microorganisms responsible of the infection include *staphylococci*, *enteric cocci*, fungi and others.

Once established, infective endocarditis is manifested by fever, vasculitis, heart murmur and septic embolism. It also can lead to serious results as damage to the heart valves, impeded heart function, heart failure, renal failure or cerebral embolism.

The condition is managed by penicillin/gentamicin combination through IV administration for four to six weeks followed by oral antibiotics for two to four weeks. In addition, a surgery may be required to repair the resultant defect.

The best management of such a case is to prevent its occurrence. Patients at high or moderate risks should receive antibiotic prophylaxis (Box 3.8), while those at low risk do not. The recommended regimen is shown in Tables 3.14 and 3.15.

Box 3.8: Patient classification according to degree of risks to develop bacterial endocarditis

High-risk
Prosthetic valves
History of previous endocarditis
Congenital heart disease (cyanotic)
- *Teratology of Fallot*
- *Transposition of great arteries*
- *Single ventricle defect*

Surgically constructed pulmonary shunts
Moderate risk
Congenital defects other than high-risk
Acquired valvular dysfunction (rheumatic heart disease)
Mitral valve prolapse with valvular regurgitation/thickened leaflets
Hypertrophic cardiomyopathy
Low-risk (antibiotics not indicated)
Mitral valve prolapse without valvular regurgitation
Previous rheumatic fever or Kawasaki disease without valvular dysfunction
Previous coronary artery bypass surgery
Cardiac pacemakers and defibrillators
Isolated atrial septal defect
Physiologic innocent heart murmurs

Table 3.15: Prophylactic oral antibiotics* against IE, agents and doses

Member	*Dosage*	
	Adults	*Children*
Amoxicillin	2 g	50 mg/kg
Clindamycin	600 mg	20 mg/kg
Cephalexin/cefadroxil	2 g	50 mg/kg
Azithromycin	500 mg	15 mg/kg
Clarithromycin		

* Administration should start one hour before operation

Patients with **previous history of infective endocarditis** have higher rates of developing vegetation and infection. In addition, they may have **prosthetic valves** installed to repair the damage induced by the previous infection, which by itself increases the possibility of developing the infection. In addition, the tissues around these prosthetic valves may get inflamed and they may get loose, which is dangerous.

Teratology of Fallot is a cyanotic heart disease associated with four defects occurring together, and these are: Ventricular septal defect, pulmonary artery stenosis, overriding aorta and right ventricular hypertrophy. The patient is seen with dyspnea, fatigue, and hypoxic episodes. Finger clubbing and polycythemia are also seen.

The patient general growth is retarded. The condition itself needs corrective surgery and is of high-risk to develop bacterial endocarditis.

Ventricular septal defect (VSD) alone is of moderate risk. It is the condition in which the left ventricle communicates with the right one. Because it is stronger, the left ventricle forces blood into the right ventricle which pumps it into the pulmonary circulation. The pulmonary pressure is increased reaching that of the systemic pressure. Blood turns back through the defect to the left ventricle (reversed shunt). The defect should be surgically corrected. Other congenital defects are of moderate risks.

Atrial septal defect, of low-risk group if isolated, is a communication between both atria which causes blood to pass from the left atria to the right one which gets dilated. Pulmonary pressure increases and the patient may complain of dyspnea. Atrial arrhythmia, fibrillation and in later stages, right sided heart failure may occur. If significant, it may need surgical correction before the age of ten years.

Acquired valvular dysfunction may follow Kawasaki's disease or the more common rheumatic heart fever. **Rheumatic heart fever** is an inflammatory disease which is common among children. It is caused by α-hemolytic *Streptococcus* reaching the heart from oropharyngeal infections. Organs other than the heart like: skin, joints and CNS are also affected. The causative bacteria induces an autoimmune reaction in which the produced immunoglobulins act by damaging the heart (endocardium, myocardium and pericardium are all affected). The damaged valves are associated with regurgitation in the blood flow. The patient complains of painful joints (migratory polyarthritis), fever, malaise, anorexia, murmurs, spasmodic movements and speech alteration (CNS), and erythema marginatum (pink skin rash with slightly raised edges). The condition is treated with penicillin and the patient undergoes monthly penicillin prophylaxis till the age of 25 years or up to five years after the initial incidence. In such patients, the choice of antibiotic prophylaxis for dental procedure should be an agent other than β-lactam group (erythromycin is a good substitute) as bacteria may be resistant to them.

Kawasaki's disease (Japan) is another acute condition affecting children. It is of unknown etiology, but a role of immune reaction is implemented. The condition is associated with fever persisting for more than five days, generalized vasculitis (including the coronary artery), unilateral lymphadenopathy, mucocutaneous and ocular lesions. Serious cardiac complications as dysrhythmia and aneurysm of the coronary artery may predispose to myocardial infarction. The condition is treated by daily aspirin (80–100 mg/kg/day) and single dose of gamma globulin.

Mitral valve regurgitation is the backflow of blood through incompetent valves into the left ventricle with atrial dilatation. It may be caused by rheumatic fever, aortic valve disease, myocarditis, infective endocarditis, and collagen disorders like Marfan's syndrome and Ehlers Danlos syndrome. The patient may complain of palpitation, dyspnea, orthopnea, and fatigue. Anticoagulants, diuretics and ACE inhibitors may be provided. A surgery to repair or replace the mitral valve is needed.

Mitral valve prolapse, another moderate risk condition, is caused by excessively large leaflets of the valves or enlarged mitral annulus (opening). Long chordae tendineae and defective papillary muscles may also be the cause. Significant regurgitation may warrant valvular surgery. However, if insignificant, drug therapy alone (anti-arrhythmia and β-blockers) may suffice and in that case, no antibiotic prophylaxis is needed.

Hypertrophic cardiomyopathy is associated with enlarged thin-walled left ventricle, which exhibits poor functions and low cardiac output. The valvular movements are reduced and the left ventricular contractions are disorganized. Syncope, dyspnea, angina, arrhythmia and even sudden death may occur. The condition is treated with antiarrhythmic, β-blockers and surgical repair.

Previous coronary artery bypass surgery to manage myocardial infarction, by reconstruction of the coronary artery with vein graft form other site of the body, is not susceptible to infection, so, no need for antibiotic prophylaxis.

Cardiac pacemakers, devices implanted in the chest with wire running through the superior vena cava to reach the right side of the heart, are also of low-risk group.

Prophylaxis against Prosthetic Joint Infections

Implanted prosthetic joints to replace damaged ones may get infected after oral procedures or even by established odontogenic infections. In these patients, infections should be managed aggressively to prevent infection and failure of prosthetic joints. Oral procedures

mentioned in Box 3.7 also apply to prosthetic joint infection. Similar antibiotic regimen is also used. However, only certain patients will require the prophylaxis (Box 3.8).

LOCAL AND TOPICAL AGENTS

To have a direct effect on the infecting microorganisms, it seems logical to apply the antimicrobial agent directly to the infected site. Natural antimicrobial compounds as immunoglobulins and salivary enzymes produce similar effects. It was also thought that the greater the systemic antibiotic concentration in serum, the more effective it is in the treatment of periodontal diseases. Local application of antibiotics, especially in the management of periodontal diseases, should maintain constant therapeutic concentration in the face of small periodontal pocket/sulcus area and the continuous washing action of the gingival crevicular fluids. If these two obstacles are managed, it would be possible to avoid the use of systemic antibiotics. In addition, the chance of tissue invasion at recall visits by instrumentation with or without surgery is reduced.

Application methods are various with different degree of success. Topical application by direct placement or mouthwash provides only transient and superficial effects. This method is used as a preventive measure, as well as, in providing transient therapeutic effects. If applied in pocket therapy, mouthwashes provide only four percent pocket penetration. The use of irrigators (supragingival or subgingival) provide deeper pocket penetration. However, the used irrigant will be washed away rapidly by the flow of gingival fluid. The installation of slow releasing device at the pocket ensures adequate concentration of the active agent at longer periods. The used local devices include polymers, dialysis tubing, chips or gels that harden on time. After the therapeutic period, these devices should be removed. In the following section, the commonly used agents in the prevention and treatment of oral infections are briefly discussed.

Chlorhexidine digluconate (0.12%), is an antiseptic agent which is active on gram-negative and gram-positive bacteria, as well

as, other microorganisms like fungi. The drug acts by membrane disturbance action. It can be used locally to reduce microbial population and interrupt plaque layer (therapeutic). It also impedes plaque formation as it adheres to the dental pellicle and prevents the adherence of bacteria, a property known as **substantivity**. The addition of fluoride adds additional anticaries as well as antibacterial effects (Table 3.16).

It is better to be used after flossing and brushing to allow chorohexidine binding to the dental pellicle and to avoid its deactivation by the anionic compounds present in the toothpaste. In addition, food and smoking should be avoided after using this agent for the same reasons. As a mouth wash, it should be used in undiluted form for 30 seconds twice daily. It is also considered as one of the best solutions for irrigation systems in concentration up to 2.5 percent. It is also used with acrylic chips or biodegradable gelatin chips for local application.

Common side effects of chlorhexidine include: staining of teeth or restorations, allergic reactions, parotid gland swelling, increased calculus formation and altered taste sensation.

Table 3.16: Prophylactic parenteral* antibiotics, agents and doses

Member	*Dosage*	
	Adults	*Children*
Ampicillin	2 g	50 mg/kg
Clindamycin	600 mg	20 mg/kg
Vancomycin†	1 g	20 mg/kg
High-risk patients		
Ampicillin +	2 g	50 mg/kg
Gentamicin	1.5 mg/kg	1.5 mg/kg**
Vancomycin† **+**	1 g	1.5 mg/kg
Gentamicin	1.5 mg/kg	1.5 mg/kg**

* Given 30 minutes before surgery.

** Child dose should not exceed adult dose.

† Given in slow IV infusion at 1 to 2 hours.

Hydrogen peroxide is a pale-blue, weak acid but strong oxidant and antiseptic. It is naturally produced by oxygen metabolism in aerobic bacteria and once formed; it is decomposed by the action of peroxidase enzymes into oxygen and water. The absence of these enzymes in anaerobic bacteria makes them unable to live in high oxygen tension environments. It is used as an antiseptic/disinfectant, cleansing agent through its effervescence, and to stop bleeding from oozing capillaries. In addition, it can be applied directly over necrotic lesions caused by ANUG and as a mouthwash. It is used also for other anaerobic infections like pericoronitis and abscess (Table 3.17).

Povidone-iodine compounds are common oropharyngeal antiseptic agents which are active on bacteria, spores, fungi and even viruses. It is used in full concentration for therapeutic uses, and in diluted form as a preventive agent. It is also applied as a scrub before surgeries (Table 3.17). This agent should be avoided in patients with thyroid diseases, cases of known allergy to the agent or in cases of pregnancy and breastfeeding.

Tetracycline compounds are also available as mouthwash, irrigant solution and cream. Tetracycline is a broad spectrum antibiotic with additional anticollagenase activity. Like chlorhexidine, it also prevents the adherence of bacteria to dental and soft tissue surfaces (substantivity). It can be used in the treatment of oral ulcers (with or without cortisone) and in the management of periodontal diseases. Local application is in the form of actisite fibers, which are nonresorbable plastic copolymer 0.5 mm in diameter, with 25 percent tetracycline powder. The releasing device is subgingivally placed, secured with an adhesive and left for 7 to 12 days. Great results are expected of reduced bleeding on probing, decreased pocket depth and improved clinical attachment level. Other agents, like doxycycline hyclate in biodegradable polymer (Atridox) and minocycline 2 percent gel (Dentomycin), have also been proven to be as effective. In addition, **metronidazole benzoate** 25 percent (gel) is packable in the periodontal pocket after which the gel form increases in viscosity to reach a hardened state. This too has been proven to be of benefits.

Table 3.17: Common topical antibiotics and antiseptics

Agent	*Form*	*Uses*
Chlorhexidine **Hexitol** **Antiseptol**	Solution	Therapeutic use Mouthwash Irrigation Maintenance of OH
	Chips	Local application
Hydrogen peroxide	Solution	Mouthwash Local application Root canal irrigant Antihemorrhagic
Povidone iodine **Betadine** **Povidin**	Solution	Therapeutic mouthwash Surgical preparation
Neomycin (with cortisone)	Cream	Same as oxytetracycline
Fusidic acid **Fusidine**	Cream	Topical antiseptic
Tetracycline	Solution	Mouthwash Irrigant
	Cream	Topical antiseptic RCT dressing Root conditioner
	Actisite fiber	Local application
Doxycycline hyclate **Atridox**	Biodegradable polymer	Local application
Minocycline **Dentomycin**	Gel	Local application
Metronidazole	Gel	Local application

Creams, like oxytetracycline or neomycin, are available for RCT dressings between appointments and for root conditioning during periodontal surgeries. They are also indicated as a dressing over traumatized skin or surgical sites in the facial area.

GENERAL CONSIDERATIONS

To gain maximum benefits, antibiotics should be used along with the removal of the cause (I and D, RCT or extraction). Debridement and drainage reduce bacterial population, amount of their toxins and tissue barriers. The blood circulation is enhanced and this allows access of both natural body immune elements and the used antibiotics to reach the infection site. Irrigation with normal saline or antiseptic solution flushes bacteria away, provides antiseptic effect and in some cases, provides organic dissolution effects (as in RCT).

Patient's compliance should be also considered. They should be provided with adequate post surgical instructions and care. Supportive treatment in the form of analgesics and anti-inflammatory drugs, high calorie diet, high fluid intake, and the use of antiseptic mouthwash should be considered, too.

Antibiotics should be chosen carefully as regards to their costs, frequency of intake and the duration of their use. Compliance is enhanced as the frequency is decreased. To attain high initial serum level, a loading dose (doubled initial dose) is used. The patient should be put on a recall visit in two to three days to allow evaluation of the provided treatment and antibiotics. Usually the condition is improved. As a rule, antibiotics should continue for two to three days after initial improvement. However, nonresponsive cases indicate incomplete or improper treatment, resistant strains or wrong antibiotics.

SPECIFIC CONSIDERATIONS

Certain conditions require specific considerations, like children, pregnancy and breastfeeding, and patients with liver or kidney diseases.

In children, quinolones, metronidazole, clindamycin (infants) and tetracyclines (below the age of 8) are contraindicated. Modification of the form and dose are presented in Table 3.18. The table also lists those drugs that can be used safely or avoided in case of pregnancy and breastfeeding. Breastfeedings should be done

Table 3.18: Showing specific considerations regarding antibiotics

Pregnancy and Breastfeeding		
Use	*Use with Caution*	*Avoid*
Penicillins Erythromycin (not estolate form) Azithromycin Cephalosporin	Clindamycin	Tetracycline Fluoroquinolones Metronidazole Clarithromycin Erythromycin (estolate form) Aminoglycosides Vancomycin

Children

Contraindicated	*Safe drugs*	*Modified dose*
Tetracyclines Metronidazole Fluoroquinolones	Penicillin V	25–50 mg/kg/day in 4 divided doses (max 3 g/day)
	Amoxicillin	
	Ampicillin	50–100 mg/kg/day in 4 divided doses (max single dose not more than 250 mg)
	Cephalexin	25–50 mg/kg/day in 4 divided dose (max 3 g/day)
	Clindamycin (not for infants)	10–25 mg/kg/day in 3-4 divided dose
	Erythromycin	10–25 mg/kg/day in 3-4 divided dose (max 2 g/day)

Kidney disease/failure

Use safely	*Modify*	*Avoid*
Clindamycin	Penicillin	Aminoglycosides
Erythromycin	Amoxicillin	Vancomycin
Clarithromycin	Clavulanic acid	
Doxycycline	Metronidazole	
	Cephalosporin	
	Ciprofloxacin	

Liver disease/failure

Use safely	*Modify*	*Avoid*
Penicillin	Clarithromycin	Tetracyclines
Amoxicillin	Clindamycin	Erythromycin estolate
Ampicillin	Metronidazole	
Cephalosporin	Augmentin	Aminoglycosides
Minocycline	Erythromycin stearate	Azithromycin

before taking antibiotics to reduce their level in breast milk. Certain drugs (tetracycline or erythromycin estolate) induce liver damage and should be avoided in liver disease. Table 3.18 lists those drugs that can be used safely, those requiring modification and those that should be avoided.

Box 3.9: Drug interaction

Antibiotics may interact with food and/or drugs if taken together. Azithromycin, ciprofloxacin and tetracycline absorption is affected by the intake of calcium (tablets or dietary), iron, magnesium, and aluminum. If must be taken, they should be taken at least two hours after antibiotics are taken to allow for their absorption. Food may enhance the absorption of other types of antibiotics like clarithromycin. With clindamycin, food decreases the degree of gastric upset. The effect of oral contraception is reduced with the intake of antibiotics (broad spectrum), as the bacteria responsible for the activation of the drug is inhibited, causing reduced level of the agent. If the patient is on contraceptive pills, she should be advised to use extra methods of contraception.

Most antibiotics enhance the effects of anticoagulant therapy. However, tetracycline decreases the effect of heparin. The concurrent intake of antibiotics and analgesic may decrease the bioavailability of antibiotic. However, diclofenac appears to increase the level of tetracycline and ibuprofen increases cephalosporin.

Certain drugs act on the liver microsomal enzyme system either by enhancing or inhibiting it. Enhancement of the hepatic enzymes causes either rapid elimination of the active drug (due to increased metabolism), or increased rate of drug activation (if the metabolites are the active components). Examples of hepatic enzyme inducers include: phenobarbital (barbiturates), carbamazepine (antiepileptic), phenytoin (antiepileptic) and rifampin (antibiotic, used for treatment of TB). On the other hand, hepatic enzyme inhibitors act on the opposite way. Examples of drugs producing such effects include: macrolides, ketoconazole (antifungal), ritonavir (antiviral for HIV treatment), and omeprazol (protein pump inhibitor used in peptic ulcers). Therefore, the level of antibiotics metabolized in the liver will be either increased with possible toxicity or decreased below the effective level. Macrolides, clavulanic acid, tetracyclines and clindamycin are metabolized in the liver, so, special

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consideration should be made before the concurrent intake of these agents along with those drugs affecting the hepatic enzymes.

Tetracyclines reduce the effect of penicillin of these two are taken together (antagonism). Aminoglycosides or clavulanic acid have synergic effect if taken with penicillins. Aminoglycosides effects are increased as the penicillins allow their intrabacterial concentration by cell wall disturbance. Clavulanic acid acts by guarding the β-lactam ring against β-lactamase enzyme. Probencid (uricosuric agent) is sometimes used to increase the level of β-lactams as it blocks tubular secretion of penicillins. Renal toxicity is enhanced if taken with dirutics.

The level of tetracycline is decreased by the concurrent intake of cimtidine (agent that reduces gastric acid secretions, used for the treatment of peptic ulcer), kaolin (antidiarrheal) and with ACE inhibitors (angiotensin converting enzyme). Tetracycline causes lithium toxicity. Tetracycline is metabolized in the liver, so concurrent intake of hepatic enzyme inducers reduces its effects. With methoxyflurane (inhalational anesthetic), the risk of renal damage is increased.

Macrolides are concentrated and metabolized in the liver and they are hepatic enzyme inhibitors, as well. They may cause toxicity of those drugs metabolized in the liver, as: theophylline (bronchodilator), carbamazepine, phenytoin, valproic acid (antiepileptics), midazolam, chlorpropamide (hypoglycemic drug), digoxin (antiarrhythmia and for heart failure) and warfarin. With lovastatin (cholesterol lowering agent), tetracyclines increase the muscle wasting effects. Cardiac arrhthymia can be produced if prescribed with cisapride (agent that reduces gastric efflux and increases gastric emptying), terfenadine (antihistamine), or pimozide (antipsychotic). Erythromycin toxicity may occur if taken with cimetidine or ritonavir.

NSAIDs increase the risks of seizures if taken with ciprofloxacin. Such effect is also possible if theophyllin is co-taken. The effect of hypoglycemic drugs may be potentiated if taken with quinolones. They may also result in phenytoin toxicity. The level of fluoroquinolones may be decreased by the intake of sucralfate (for peptic ulcers) or calcium. If taken with cyclosporine (immune suppressant), renal toxicity is enhanced.

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Metronidazole causes lithium, fluorouracil (anticancer) and phenytoin toxicities. Hypoglycemic effects may be potentiated, too. If taken with alcohol, metronidazole causes an antabuse effect or disulfiram reaction (flushing of skin, rapid heart beats, confusion and fainting). Its metabolism is in the liver, so care should be taken in those with liver disease or taking drugs that act on the hepatic enzymes.

Aminoglycosides, nephrotoxic, and such effect is further increased of taken with diuretics as mannitol (osmotic diuretic), frusemide (loop dirutic) or amphotericin (antifungal). Ototoxic effects may also be potentiated. Aminoglycosides decrease the effects of corticosteroids. They act synergistically with β-lactams and vancomycin.

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Chapter 4

Antimicrobial Agents Used in Dentistry: Antifungals

INTRODUCTION

FUNGAL INFECTIONS

Fungi are eukaryotes; this means that they have cells with higher internal organization when compared to bacteria. A fungal cell has a cell membrane, DNA double helix and other organelles like endoplasmic reticulum and Golgi apparatus. Of special interest is the cell membrane which is composed of proteins and phospholipids, just similar to the human cells. This similarity is responsible of the toxic effects of most antifungal agents. However, fungal membranes differ from human one in the type of sterol content. Where ergosterol is the main sterol of fungal cell membrane, the human cells have cholesterol. Fungi also possess chitin cell wall, in contrast to bacteria which have peptidoglycan cell wall, a difference which indicates that antibiotics are not usually effective on fungi.

Although present as normal flora of the skin and mucous membranes, fungi are responsible of a number of infections. Such infections may be superficial, confined to skin and/or mucous membranes, or systemic which involves the internal body organs like the lungs. Fungal infections may be caused by either opportunistic

or pathogenic species. Most fungal infections are opportunistic in nature, occurring as a result of reversed symbiotic relationship with other microorganisms or due to depressed body immunity.

The most common fungal species include *Candida albicans*, *C. glabrata*, *C. tropicalis* and *C. pseudotropicalis*. Under the microscope *Candida albicans* are gram-positive showing budding and pseudohyphae. Candida act by fermenting glucose and maltose, so candidal infections may be associated with cases of poor oral hygiene or in case of elevated salivary glucose level. Other causes of fungal infections are listed in Box 4.1.

Once established, fungal infections cause tissue damage by one or more of the following routes: (1) induction of a delayed hypersensitivity reactions by their antigenic structures, (2) the release of destructive enzymes, like phospholipase, and (3) the production of mycotoxins. Inflammatory response soon follows with the

Box 4.1: Factors predisposing to fungal infections

Systemic Factors

Conditions of depressed immunity

- AIDs
- Immunosuppressive drugs
- Malignancy
- DiGeorge syndrome
- Uremia
- Liver disease

Extremes of age (*newborn/elderly*)

Drugs

- Steroids and immunosuppressants
- Broad spectrum antibiotics
- Anticholinergics (xerostomia)

Endocrinopathies

- Diabetes
- Hypothyroidism
- Hypoparathyroidism
- Polyendocrinopathy

Contd...

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Blood dyscrasia
• Anemia
• Neutropenia
• Leukemia
• Lymphoma
Malnutrition (deficiency of folic acid, iron, vitamin C or B)
Local Factors
Repeated trauma
Excessive smoking
Bad oral hygiene
Xerostomia
Prolonged use of topical antiseptics
Topical steroid application
Increased salivary acidity
Moisture or humidity*
Denture use

* Applies to cutaneous lesions and angular cheilitis.

accumulation of inflammatory cells, edema and induction of epithelial cells to produce hyperplasia.

For a fungal infection to be managed, the causative local or systemic factors (Box 4.1) should be identified and eliminated first. A topical or systemic antifungal agent, or both, can be used. In the following is a review on the topical and systemic agents that are used to treat fungal infections.

ANTIFUNGAL AGENTS

The most commonly used antifungal agents are listed in Box 4.2.

Amphotericin B

This agent is a double bonded macrolide, naturally produced by *Streptomyces nodosus*. Its effect is dose-related, being fungicidal at sufficient doses.

It acts by forming pores as it binds to ergosterol. The formed channels cause leakage of fungal contents, mainly potassium, which causes fungal cells to deteriorate. The agent may also select human

Box 4.2: Various antifungal agents

POLYENES
- Amphotericin B
- Nystatin

AZOLES

Imidazoles
- Clotrimazole
- Miconazole
- Ketoconazole

Triazoles
- Fluconazole
- Itraconazole

cholesterol for binding and this may be the reason behind toxic effects of the drug. Amphotericin is effective on *Candida*, *Cryptococcus*, *Aspergillus*, and *Histoplasma* species. Resistant strains like *C. Lusitaniae* and *Pseudallescheria boydii* were reported. Such resistance may be due to alteration in the target ergosterol content in the fungal cytoplasmic membrane.

Amphotericin is poorly absorbed from the GIT, so it is used either topically or in intravenous form. It is metabolized in the liver and excreted in bile and urine. In liver and/or renal diseases, the dose should be adjusted. In healthy adults, the dose should not be more than 1.5 mg/kg (Table 4.1).

Common adverse reactions to amphotericin are mainly due to binding to the sterol cholesterol of the human cells. These can be

Table 4.1: Polyene antifungals

Agent	*Form*	*Dose*
Amphotericin B	IV	0.3 mg/kg/ 4–6 h
Fungizone	O. susp	50–100 mg QID/2 W
Nystatin	Drops	
Mycostatin	Pastilles	100,000 u/ml
Fungistatin	Lozenges	QID
Antimycot	O. susp	
	Ointment	

immediately observed (acute) or seen after some time on long-term use (chronic). Immediate adverse effects start at one to three hours after the drug intake and include fever, chills, nausea, hypotension, headache and thrombophlebitis. Corticosteroids, as hydrocortisone, and paracetamol may be administered to inhibit or minimize such effects. Thrombophlebitis may necessitate the use of heparin.

Long-term effects include nephrotoxicity, anemia and neurologic manifestations like impaired hearing and convulsions. Renal effects include loss of magnesium and potassium due to affected tubular functions. Such effects may need adequate hydration in the form of IV saline before amphotericin administration. Nephrotoxic drugs, like aminoglycosides or cyclosporin, should be avoided. Decreased RBCs production with the resultant normochromic-normocytic anemia may result. Such effect may be potentiated by the use of Zidovudine antiviral therapy.

Nystatin

This antifungal agent is originally developed from *S. noursei*. It was first developed in New York State. It is poorly absorbed from the GIT and has toxic effects if provided via the intravenous route. Therefore, its use is limited to topical application (Table 4.2). Available in the form of cream, troches, or oral suspension, nystatin is effective on *Candida albicans* infections, which are the most common fungal infections. This agent acts in a manner similar to amphotericin B. Adverse effects to nystatin include GIT troubles like nausea, vomiting and diarrhea which are mainly due to poor absorption. Attention to sucrose content should be paid as it may interfere with blood sugar control in diabetes and may predispose to dental caries.

Azoles

These are fungistatic agents with wide range of activity. They act by a process that involves blocking of the cytochrome P450 enzyme. This enzyme is required to convert lanosterol to ergosterol. The end result is depressed ergosterol synthesis and, hence, cell membrane

Table 4.2: Imidazole antifungal agents

Agent	*Form*	*Dose*
Clotrimazole		
Canesten	Cream	3–5/day/2 W
Canestan	O. susp	
Locasten*	Cream solution	
Miconazole		
Miconol	Cream	TID/2 W
Mykotral	Solution	
Miconaz H*	Gel	
Micoban*	Gel	
Daktarin O	Gel	
Ketoconazole	**Tablet**	**Adults**
Tocon	,,	200–400 mg/day/for
Kizol	,,	2 W
Fungizol	,,	**Children**
Nizoral	,,	5–10 mg/kg/day for 2 W

* With hydrocortisone 1 percent.

disturbance. The human hepatic microsomal enzyme system may be affected and this contributes to disturbed metabolism of other drugs and drug interactions. In addition, the human steroid hormone synthesis may be affected.

Resistance to azoles may be due to altered target enzyme and/or increased pumping of the agent out of the fungal cytoplasm. Imidazoles group includes mainly ketoconazole, clotrimazole and miconazole. Table 4.2 shows the form, dose and brand names of these agents. Triazole agents include fluconazole and itraconazole. They are shown in Table 4.3.

Ketoconazole

Ketoconazole is a broad spectrum antifungal useful in the treatment of blastomycosis, coccidioidomycosis and histoplasmosis, and chronic mucocutaneous candidiasis.

Table 4.3: Triazole antifungal agents

Agent	*Form*	*Dose*
Fluconazole **F-zole** **Fluzone** **Triconal**	Capsule	50–150 mg /day/7 days.
Diflucan	100 mg Vial	50 ml IV (2 mg/ml)
Itraconazole **Itrapex** **Itranox** **Itracon**	Capsule	100 mg/day/2W

It is available in both the topical and systemic forms. Oral tablets of this agent need acidic environment for proper absorption through the gastric lining. So, conditions of hypochlorhydria or achlorhydria, where there is decreased or absent secretion of HCl from stomach, are associated with reduced ketoconazole absorption unless placed in some sort of acidic medium. In addition, drugs or meals that elevate the stomach pH will act in the same way, so, should be avoided. This would include H2-histamine receptor blockers, antacids and diary products. Ketoconazole is metabolized in the liver and considered hepatotoxic.

Adverse effects of ketoconazole use include GIT troubles, hepatic enzyme induction and hepatotoxicity, decreased steroid synthesis with the resultant impotence, decreased libido, menstrual disturbances and gynecomastia. Drug interactions with ketoconazole are indicated in the drug interaction (Box 4.4).

Miconazole

Miconazole has similar spectrum and mechanism of action as ketoconazole; however, it is used only topically or in the IV form. It is less effective than amphotericin but with more serious adverse effects. Its applications are mainly for severe systemic or chronic mucocutaneous candidiasis. It has mild antibacterial effects, a property that makes this agent especially useful in case of angular cheilitis. Adverse effects to miconazole include GIT disturbance, rashes, fever and chills.

Clotrimazole

This agent has several advantages. First, it has the ability to bind to oral tissues and gets released later at slower rate, a property that prolongs the time of contact between the antifungal agent and the target lesion. Second, it has effects on microorganisms other than fungi, like corynebacteria and protozoa. It also proved to be useful in the prevention or treatment of noninfection diarrhea. Adverse effects to the agent include irritation, burning sensation and rashes.

Fluconazole

Fluconazole is a drug of choice to treat deep and mucocutaneous candidiasis. It is a wide spectrum antifungal agent and is present in the oral and IV forms (Table 4.3). In contrast to ketoconazole, the oral form is not affected by alkaline environment or food. Because it has lesser effects on the cytochrome P450 enzymes, fluconazole also has lesser adverse reactions and drug interactions.

Fluconazole is well distributed in the body tissue and is able to reach the CNS. It is poorly metabolized, so should be avoided in kidney disease.

Although of wide range of activity, resistant strains, like *C. galabrata* and *C. krusei*, have been discovered.

Adverse reactions to fluconazole include GIT troubles, headache and drowsiness. Depletion of potassium may also occur, so potassium supplement may be required.

Itraconazole

This potent, broad spectrum antifungal agent is considered one of the first agents against systemic mycosis. Like fluconazole, itraconazole has lesser endocrine adverse effects. In the capsule form, acidic environment and food appear to enhance its absorption. However, the suspension form (used to treat esophageal lesions) may be interrupted by food and antacids.

Itraconazole is metabolized in the liver and care should be practiced in case of liver disease. It has lesser effects on the renal system, so in case of renal disease, no dose adjustment is required.

All azole agents should be avoided in pregnancy (*see* special consideration).

Adverse reactions include GIT problems, rashes, hypertension, headache, edema, and depletion of potassium.

CLINICAL USE OF ANTIFUNGAL AGENTS

Fungal infections, related to oral and perioral tissues, are listed in Box 4.3. The aim of this section is to briefly describe the common forms of fungal infections and how to treat them. The reader is advised to refer to textbooks of medicine for further details.

Oral thrush: Pseudomembranous candidiasis is common in new born babies, elderly asnd in conditions of iron deficiency. Steroid or antibiotic use can also be possible causes. HIV should be suspected if no causative factor is clinically identifiable.

Box 4.3: Clinical use of antifungals

Superficial mycoses

Acute

- Pseudomembranous candidiasis (thrush)
- Erythmatous candidiasis
- Angular cheilitis

Chronic

- Hyperplastic candidiasis
- Atrophic candidiasis
- Median rhomboid glossitis
- Mucocutaneous candidiasis

Deep mycoses

- Histoplasmosis
- Blastomycosis
- Mucormycosis
- Aspergillosis
- Cryptococcosis
- Coccidioidomycosis
- Paracoccidioidomycosis
- Pneumocystosis

Clinically, the lesions are in the form of patches or flecks with white-yellow covering pseudomembrane that can be easily wiped off. A red base is left on wiping off such lesions, which can be quite painful. Most commonly affected sites include soft palate, cheek mucosa, vestibules, gingiva and the tongue.

The condition should be differentiated from other lesions like those occurring as a result of burns, mechanical trauma or chemical injuries as they may be of similar clinical appearance. Careful history usually reveals the cause. Oral thrush may also resemble mucous patches of syphilis which appear as discrete, small and painless lesions. Candidal infection is more diffuse and often painful on scraping. Superficial bacterial lesions, as *staphylococcal* or *gonorrheal* infections, may be differentiated on the basis of laboratory investigation. Candida have the characteristic appearance of pseudohyphae and spores. Necrotic ulcers caused by systemic disease or gangrenous stomatitis may be confused with candidal lesions as both have common systemic involvement. However, candidiasis is usually more superficial.

Once diagnosed, the underlying predisposing factors should be determined and corrected. Appropriate laboratory investigations are recommended. Topical antifungals like nystatin, amphotericin or miconazole have been tried but they were found of limited value, possibly due to poor patient compliance and poor contact with the target lesion. The use of systemic antifungal agents, like fluconazole or itraconazole, for two weeks is more effective. Chlorhexidine mouthwash is useful, too. Persistent or recurrent lesions may be associated with uncorrected predisposing factor. The condition may turn into chronic form (CMC). In these infections, HIV probability is high.

Acute erythmatous candidiasis: This form is often associated with steroid or antibiotic use. Systemic use of these agents produces localized lesions, whereas topical application is associated with more diffuse involvement.

To correct such factors, consultation regarding antibiotics should be made. The effects of topical steroid can be minimized by

gargling with water after each application. Topical agents may be used to treat such conditions. Systemic agents are useful for patients with impaired immunity.

Angular cheilitis: Inflamed, erythmatous and ulcerated angles of the mouth is known as angular cheilitis. The main cause is humidity which favors fungal proliferation. Such humidity is created by saliva which may be leaking as a result of incompetent labial seal or reduced facial vertical dimension in association with dentures. Lip licking habit may also be the cause. Angular cheilitis may be associated with intraoral lesions, commonly with denture sore mouth. The condition may also be caused by deficiency of vitamin B.

The diagnosis of the condition is straightforward. However, it may be associated with *Staphylococcus aureus* infection. Such pathogen may be inoculated from the nose and it is associated with more redness and possibly bleeding. To confirm, a separate smear from each angle/nares is performed.

Oral lesions, when present, should be treated as they act as a reservoir of fungi. Angular cheilitis is treated with miconazole cream applied to the angles of the mouth. Fortunately, miconazole is also effective on *S. aureus*, so, it can be used in case of mixed infection. If the lesion is purely bacterial in origin, it should be treated with fusidic acid cream applied every six hours.

Chronic hyperplastic candidiasis: This white lesion is similar to leukoplakia in that it cannot be wiped off and, may have premalignant potential. The lesion can be a mixture of a leukoplakia along with fungal infection. It commonly affects the cheek mucosa or the dorsum of the tongue. Epithelial alteration may be secondary to the fungal infection; however, it is possible that fungal infection is secondary to epithelial alteration. Excessive smoking is a usual finding, and the patient may have suffered from previous episodes of denture stomatitis and/or angular cheilitis. A biopsy is indicated in this case to exclude malignancy and to confirm the diagnosis. The microscopic appearance may reveal fungal hyphae, hyperplastic epithelium with or without dysplasia along with chronic inflammatory cells.

The fungal component is treated by the use of a systemic antifungal; like itraconazole or fluconazole for about three weeks. This is more effective than the use of polyene agents which require longer period and more patient compliance. Persistent epithelial alteration indicates excision and histologic examination.

Chronic atrophic candidiasis: Chronic erythmatous form of candidal infection is associated with the improper use of dental appliances, especially removable dentures. Dentures are either continuously worn or the patient is not careful about oral hygiene. Continuous wearing of dentures provides areas isolated from saliva and oral environment, which favors fungal proliferation. The fitting surface of the used appliance is loaded with layers of fungal plaque, which may deeply infiltrate its bulk. The associated lesion is erythmatous with clear demarcations that clearly indicate the configuration of the used appliance. Patients complaints are usually minimal, however, when reported they are in the form of discomfort or burning sensations. White flecks or angular cheilitis may be also associated with such lesions. The condition may be confused with contact allergy, where all tissues in contact are irritated and not strictly demarcated by denture boundaries. In addition, allergy may be confirmed by epicutaneous tests.

The condition is managed by correction of the underlying factors. The used appliance is cleaned with sodium hypochlorite solution overnight for three weeks. Those with metal parts are better cleaned and soaked in chlorhexidine solution to avoid corrosion. The appliance should be removed from the mouth for eight hours per day to provide tissue rest. The fungal infection is treated by the use of topical agent (amphotericin, nystatin, or miconazole) applied both to the oral lesion and the fitting surface of the associated appliance for four weeks.

Median rhomboid glossitis: It was considered that MRG is of developmental etiology with the partial persistence of tuberculum impar. However, its recurrent nature and absence in children along with its resolution with the use of antifungal therapy supports its relation to fungal infection. It appears as a rhomboidal depapillated

lesion that lies just anterior to the circumvallate papilla. Another similar lesion may be seen in the opposing palatal tissue, possibly due to toxic response to the lesion on the tongue, a condition known as "kissing disease". The lesion is usually asymptomatic. Smear or culture may be made to confirm the diagnosis, although, the clinical appearance is characteristic. The differential diagnosis may include squamous cell carcinoma, erythroplakia, and geographic tongue.

Topical antifungal agents for prolonged periods (up to 3 months) may be the treatment of choice. Better results are expected from the systemic application in shorter duration. The underlying systemic condition should be examined to role out any associated diseases.

Chronic mucocutaneous candidiasis: This form of candidal infection represents a form of deep infection that involves deeper parts of skin and mucous membranes. It is recognized to be resistant to treatment and it is difficult to manage. Several causes have been implemented, and accordingly, several types exist. In Type I, which is known as the familial or the limited type, the lesions are mild but appear since birth, and are known to be persistent. Sidropenia (iron deficiency) may be another finding. Iron supplements along with systemic antifungal agents are the required treatment of this form.

Type II or the diffuse type is characterized by the disfiguring granulomatous lesions which diffusely involve skin and mucous membranes. Immune defects may be an associated finding. The risk of developing secondary bacterial infections, like superficial and pulmonary infections, is high. The condition needs systemic antifungal (itraconazole) along with an antibiotic to guard against bacterial infections.

Type III, or the endocrinopathy candidiasis syndrome, is mild but exhibits a persistent candidial infection which is followed by multiple glandular dysfunctions later in life (10–15 years). It is believed that such dysfunction is caused by specific autoantibodies

directed to several glandular tissues. The commonly affected glands include adrenal glands (Addison's disease), parathyroids (hypoparathryroidism), thymus (DiGeorge syndrome). The condition requires medical management of the multiple glandular dysfunctions and a systemic antifungal.

Candidiasis thyoma syndrome is the 4th type of this group and is known as the "late onset mucocutaneous candidiasis". A tumor of the thymus gland is present and it should be surgically removed.

Systemic mycosis: This means that the fungal infection has reached deeper sites in the body tissues and organs. It may affect healthy individuals, where it is asymptomatic and self-limiting. In those with poor immunity, however, the disease is progressive, disseminated and possibly fatal. The infection may involve the lungs, maxillary sinuses and other organs. It is associated with a granulomatous lesion with abscess formation. Orally, the lesion may appear as a nodular tumor-like mass or chronic oral ulcer with bizarre configuration. History usually reveals defective immunity and/or travel to an endemic area. Smear, culture, X-ray on the chest and MRI are further useful investigations. Systemic antifungal is the treatment of choice.

GENERAL CONSIDERATIONS

All fungal infections should be treated with suspension of underlying systemic or local factors. As a rule, when no obvious underlying factor can be determined, AIDS should be suspected. It is the identification and correction of these factors which provides the definite treatment. The antifungal part of the management provides the way towards elimination of the incident infection, but not preventing it from recurrence, and sometimes, fails to eradicate the infection due to the persistence of the underlying factors.

Superficial lesions, especially in healthy individuals, are managed by topical agents for at least of two weeks after clinical resolution. It appears, however, that compliance to topical agents is low as it has longer duration, more frequency and needs greater attention.

Table 4.4: Showing specific considerations regarding antifungal use

Pregnancy and Breastfeeding		
Use	*Use with caution*	*Avoid*
Nystatin	Clotrimazole (in 2nd or 3rd trimesters)	All azoles (teratogenic should not be used in children below the age of 2 years)
Liver/renal disease	**Use**	**Avoid**
	Nystatin	**Azoles***

*Heptatotoxic agents.

To prevent recurrence, deep or systemic mycoses require the use of systemic antifungals for at least one to two weeks after clinical resolution. In chronic forms, it may need up to four weeks of antifungal therapy to completely eradicate the infection. Systemic antifungal can be used in case of recurrent or persistent infections, as well as, in case of compromised immunity.

Chlorhexidine mouthwash is a valuable adjunct to antifungal therapy as it is fungicidal, as well as, interferes with fungal adherence to oral tissues.

SPECIFIC CONSIDERATIONS

Specific considerations regarding pregnancy and breastfeeding, liver and kidney diseases are presented in Table 4.4. Possible drug interactions are indicated in the drug interaction Box at the end of this chapter.

Azoles should not be used in case of pregnancy, liver or kidney disease, cardiac diseases (as they may precipitate cardiac failure).

Box 4.4: Drug interaction

Most interactions occur with the systemically applied agents. The effects of amphotericin B are decreased if combined with ketoconazole, as the former acts on the ergosterol part of fungal membrane, whereas the latter acts by inhibition of membrane synthesis.

The azoles are P450 enzyme inhibitors; therefore, their use may cause toxicity of those metabolized in the liver. This includes

Contd...

Contd...

cyclosporin, phenytoin, tolbutamide or warfarin. Rifampicin is hepatic enzyme inducer and it causes rapid elimination of ketoconazole and, hence, less effects.

The same could occur when any enzyme inducer used along with an azole agent.

Ketoconazole absorption is decreased by the use of H_2 inhibitors, antiacids or alkaline food stuff. Antimuscarinics like scopolamine, hyoscine or atropine may also interfere with absorption of azoles.

Grapefruit juice may hamper the absorption of itraconazole.

Azoles may cause cardiac dysrhythmia if taken with terfenadine, astemizole or cisapride. They also act by inhibiting the metabolism of oral anticoagulant, statins (cholesterol lowering agent) or quinidine. The use of statins is also associated with increased myopathy. The oral contraceptive effect may be reduced with the use of azole agents. So, extra means of birth control measures should be advised.

The azoles should not be coadministered with those nephrotoxic agents so as not to increase the burden on the kidneys.

They may also precipitate acute attacks of porphyria (porphyrin disorder) in susceptible patients.

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Chapter 5

Antimicrobial Agents Used in Dentistry: Antiviral Agents

INTRODUCTION

VIRAL INFECTIONS

Viruses are obligate intracellular parasites, which live and depend on other living cells for their replication. Viruses are simple in their structure being composed mainly of three compartments; namely a nucleic material, protective protein coating and certain enzymes essential to start their replication.

The protective protein coat, also known as the nucleocapsid, protects the viral genetic material and plays a role in viral attachment and penetration into the host cells, possibly through the glycoprotein spikes present on its surface. Viruses attach to certain cellular receptors and this may explain the cellular selectivity of certain viruses (Table 5.1). Entry may occur either by fusion of the virus with the host membrane or by the process of endocytosis.

Regarding the nucleic acid content, viruses contain either DNA or RNA but not both. In addition, these materials can be either single stranded (SS) or double stranded (DS). Inside the

Table 5.1: List of viruses with examples of pathological lesions they produce

Virus	*Target tissue*	*Associated infection/ disease*
HERPES VIRUSES		
HHV1 (HSV1)	Oral epithelial cells Neural tissues	PHGS Recurrent herpetic lesions
HHV2 (HSV2)	Genital epithelial cells Neural tissues	Genital herpes
HHV3 (HZV)	Same as HHV1	Chickenpox (Varicella) Shingles (zoster)
HHV4 (EBV)	Glandular tissue Respiratory tract Lymphocytes	Glandular fever Hairy leukoplakia Burkitt's lymphoma
HHV5 (CMV)	Oral epithelium Lymphocytes	Glandular fever
HHV6	T-lymphocytes	Glandular fever Persistent lymphadenopathy Chronic fatigue syndrome
HHV7	T-lymphocytes	As a cofactor with HHV6
HHV8		Kaposi's sarcoma Body cavity-based lymphoma
ENTEROVIRUSES		
Coxsackie viruses A	Epithelial cells	HFMD Herpangina
Coxsackie viruses B		Herpangina
PARAMYXOVIRUSES		
Measles (rubeola)	Respiratory tract	Measles
Measles (rubella)	Any other tissue	German measles
Mumps		Mumps
HUMMAN PAPILLOMA VIRUS (HPV)	Epithelial tissue	Squamous cell papilloma Condyloma Carts
RETROVIRUSES (HIV)	CD4 on T cells	AIDs

HHV = Human Herpes Virus, HSV = Herpes Simplex Virus, HZV = Herpes Zoster Virus, EBV = Epstein Barr Virus, CMV = Cytomegalovirus, PHGS = Primary Herpetic Gingivostomatitis, HFMD = Hand Foot and Mouth Disease.

host cell, the genome gets uncoated and the process of gene transcription and synthesis of nucleic material and protein coating is initiated.

The enzymes present are just to direct the host cellular ribosomal system to their demands. Polymerase enzyme is the main viral enzyme and it initiates the polymerization reaction for the synthesis of viral nucleic material.

Virally infected cells get exhausted and their functions as well as their structures are deteriorated. Cellular damage or lysis may be due to the action of cytotoxic cells which recognize viral polypeptides on the infected cell surface. The production of auto-antibodies by β-cells may affect unrelated cells and produce lesions inconsistent with the site of infection. The production of hyperplastic or neoplastic lesions may be due to the cellular response to their new function as machinery for viral replication.

It should be noted that viral infections are associated with spread and replication of the virus before their manifestations appear, an important point to consider in the treatment of viral infections. Once the manifestations appear, the use of antiviral agents is of limited value. This signifies the prodromal signs and symptoms as the use of antiviral agents is the best at this stage of the viral infection.

INDIVIDUAL DRUGS

Box 5.1 lists the most commonly used antiviral drugs in the dental practice. Antiviral agents mainly act as analogs to essential viral molecules to stop their replication.

Nucleotide Analogs

A nucleic acid is a polymer of many nucleotides. Nucleotides themselves are made up of three components and these are: A monosaccharide, a nitrogenous base and a phosphate group. The nitrogenous bases are either single ringed (pyrimidines) or double ringed (purines). Pyrimidines are uracil, cytosine or thymidine, while the purine bases are either adenine or guanine.

Box 5.1: Antiviral agents most commonly used in dental practice

Nucleotide analogs
- Acyclovir
- Valacyclovir
- Penciclovir
- Famciclovir
- Ganciclovir
- Cidofovir

Pyrophosphate analogs
- Foscarnet sodium

Recombinant proteins
- Interferon-α

The antiviral analogue acts by substituting the natural nitrogenous bases with nonfunctional synthetic analog resulting in termination of the polymerization reaction and the production of nonfunctional genetic strand. This would stop viral replication.

Acyclovir. This is a purine base analog which uses guanosine. It gets activated by the enzyme thymidine kinase which is coded for, by the viral genes. In this way, acyclovir exhibits high concentration in virally-infected cells. Thymidine kinase catalyzes phosphorylation reaction which converts acyclovir into acyclovir monophosphate. The drug is further phosphorylated by the host enzymes into di- and triphosphated forms. The final form competes with guanine for the viral DNA polymerase. Once attached to the polymerizing DNA, the agent soon stops the reaction. The agent may cause the polymerase enzyme to loss its function too.

Acyclovir is most effective on those viruses which encode for their own thymidine kinase like HSV and HZV. Other viruses like CMV or EBV are less susceptible. Resistance to acyclovir has been attributed to the lack of thymidine kinase or polymerase enzyme.

The drug is partially metabolized and gets eliminated by means of the renal system. This notifies care when used in patient

with renal disease as acyclovir may get accumulated and causes toxicity. Therefore, acyclovir dose should be adjusted.

Acyclovir is present in the topical, oral and intravenous forms (Table 5.2). Topical cream, ointment or swish and swallow solutions can be used for mild cases. Local reaction to the topical agent may be expected, however, the oral form is indicated for more severe infections or in those with depressed immunity. Due to limited oral absorption of acyclovir, IV form may be more reliable in severe cases with history of depressed immunity.

Because of higher affinity to virally infected cells, acyclovir use causes minimal adverse reactions which are basically route-dependant. Local irritation is expected to the topical form, while GIT irritation and headache to oral form. In higher doses of the IV form, transient renal dysfunction is expected. Acyclovir may cause renal tubular obstruction as it is excreted in the crystalline form. Rehydration is an important step before the administration of IV acyclovir, especially in case of dehydration.

Valacyclovir. The addition of valyl easter to acyclovir resulted in 3 to 5 folds increase in its bioavailability. Valacyclovir is only present in the oral form and possesses the same spectrum and mechanism of action as acyclovir except for its greater tissue

Table 5.2: Acyclovir and valacyclovir

Agent	*Form*	*Dose*
Acyclovir		
Virustat	5% Cream	Applied 5 times per day
Zovirax	5% Cream	
	Suspension	5 ml (400 mg)/5/day
	Tablets	400 mg/5/day
	Vial (IV)	250 mg/5/day
Acyclovir	Ampule (IV infusion)	1 g/5/day
Valacyclovir		
Valtrex	Tablet	500 mg/bid

concentration (Table 5.2). The compound is broken apart into the active form in the GIT and liver. Therefore, GIT side effects are not uncommon.

Penciclovir. This antiviral agent is an acrylic guanosine nucleotide analog which undergoes similar mono-phosphorylation, as acyclovir, by the enzyme thymidine kinase. Penciclovir is present only in the topical form and it has about 20 to 30 times longer duration of action than acyclovir (Table 5.3). It also can produce higher intracellular concentration. This would reduce the frequency of application which enhances patients' compliance. It has the same spectrum as acyclovir. The adverse reactions to this agent are minimal.

Famciclovir. This agent is the prodrug of penciclovir, made to allow its use via the oral form. It is a deoxyguanosine analogue which by means of the GIT and liver undergoes deacetylation process, converting it into the active form. Famciclovir exhibits excellent GIT absorption and has 3 to 5 times higher bioavailability than acyclovir (Table 5.3). This agent is suitable for HZV infections, although effective for the HSV, too. Adverse reactions to the drug are minimal except for nausea and headache.

Ganciclovir. Ganciclovir is a similar analogue to acyclovir but it is a good substrate for the enzyme phosphotrasferase which is present predominantly in CMV. It is a potent antiviral agent with activity about 8 to 20 times that of acyclovir. Due to its serious side effects, its use is preserved for serious viral infections caused by CMV, as CMV retinitis in HIV patients. Its use may also be justified in for the prevention of CMV infections in organ transplantation or HIV patients.

Table 5.3: Penciclovir and famciclovir

Agent	*Form*	*Dose*
Penciclovir	1% Cream	every 2 hours
Famciclovir		
Famvir	Tablet 250 mg	2–3 times/day
Propencivir	Tablet 500 mg	2–3 times/day

Table 5.4: Doses/forms of ganciclovir

Agent	*Form*	*Dose*
Ganciclovir	IV	10 mg/kg/day Or 500 mg/6 hours
Cymeven	Tablet	250–500 mg/bid
Valacyte	Tablet	450 mg /bid

Ganciclovir is present in three forms; intravitreal, oral and intravenous. For the treatment of CMV retinitis, intravitreal injection of ganciclovir every six months is the treatment of choice. In case of serious CMV infections, ganciclovir is used in the IV form. Oral form is used as a maintenance therapy (Table 5.4).

Adverse reactions include bone marrow suppression with the resultant anemia, neutropenia and thrombocytopenia. It is also toxic to the kidneys and the nervous system. Other effects include nausea, diarrhea and flatulence. The drug is teratogenic, embryotoxic and carcinogenic in experimental animals, so should be avoided in pregnancy.

Cidofovir. This single-ringed cytosine analog acts only on DNA viruses by inhibiting their polymerase enzymes. Because of its effects on the renal system, it is only approved to be used in case of severe CMV infections, especially in those with HIV. To reduce renal toxicity, probenecid and saline solution should be administered. Cidofovir is present in topical gel, intravenous and intravitreal forms. Its use should be avoided in case of renal disease.

Pyrophosphate Analogs

Foscarnet Sodium

This is a pyrophosphate analog which acts on the DNA polymerase with the resultant blockade of the DNA/RNA chain and by the formation of nonfunctional complexes. Foscarnet

sodium is not a nitrogenous base, so, its effect is not dependant on the presence of an activating enzyme. This feature makes it useful in case of acyclovir-resistant viruses and CMV infections. However, resistance to foscarnet has been described and it is attributed to gene mutations which result in altered target. It is present in IV and oral forms. The associated adverse reactions are common despite its low affinity for host polymerase enzymes. Renal failure, electrolyte imbalance, nausea, vomiting, anemia and seizures are expected.

Recombinant Proteins

Interferon is a glycoprotein naturally produced in response to viral infections and bacterial endotoxins. In response to viral infections, interferon acts by inducing cellular enzymes, namely endonucleases, which act by degrading viral mRNA and, thus, preventing viral replication. Interferon also acts by increasing the number of natural killers and the expression of viral antigens. The agent is present in several forms (Table 5.5). IV/IM forms are generally indicated for chronic hepatitis B and C. Intralesional form can be used to treat venereal warts caused by HPV, while the submucous one is used to treat other oral virally-related lesions like Kaposi's sarcoma and oral hairy leukoplakia. Interferon is not present in the oral form as it is unstable in the gastric environment. Common adverse reactions include flu-like symptoms, hypotension, myelosuppression, autoimmune disorders (like thyroiditis), neurotoxicity and psychiatric disorders.

Table 5.5: Doses and forms of interferon

Agent	*Form*	*Dose*
INF-α2B **Intron-A** **Roferon-A** **Egyferon**	IMSC	3 million IU

CLINICAL USE OF ANTIVIRAL DRUGS

The most common viral infections related to the oral cavity are caused by HSV and HZV (Table 5.1). Oral lesions produced by Coxsackie virus are also well recognized, but they usually do not require the use of antiviral agents. In the following, it is a brief description of the common viral lesions along with the way of managing them.

PHGS. This acute condition can be due to HSV_2 or more commonly, HSV_1. It can affect either children or adults, in the form of mild or severe forms. The oral lesions are preceded by discomfort which changes later into vesicles and ulcers. What characterizes AHGS ulcers is that they are shallow, painful and involve the nonkeratinized mucosa. The nutritional state of the patient may be altered and the affected children are usually dehydrated.

The patient or parents should be informed about the infectious nature of the disease (to prevent spread of the infection to other body sites or to other family member) and care should be practiced while handling these patients (to avoid herpetic whitlow).

The condition is self-limiting and usually resolves in 10 days. In immunocompetents and in its simple forms, PHGS requires only symptomatic treatment (Table 5.6). However, swish and swallow preparations of acyclovir may accelerate healing. In case

Table 5.6: Selection and regimen of antiviral for **PHGS**

Lesion form	*Agent and Dose*
Simple form in healthy patient	Self-limiting disease Topical acyclovir 5%/5/day
Severe or unresponsive forms	Acyclovir 200–400 mg/tid/10 days Valacyclovir 1 g /bid/10 days Famciclovir 250 mg/tid/10 days Penciclovir (topical)/2 h/7 days*
Defective immunity	Valacyclovir 1 g/tid/7 days Famciclovir 500 mg/bid/7 days Acyclovir (IV) 5 mg/kg/8 h/7 days

*Applied in addition to the oral forms.

of severe, nonresponsive lesions, or in those with high susceptibility to severe complications (like those with defective immunity or those with eczema or skin burns), systemic antiviral is needed.

Recurrent herpetic lesions. HSV remains dormant, or in state of chronic infection, in the sensory neural ganglia. The dormant viruses remain protected from the immune factors there and once activated (by stress, sunlight, trauma, etc.), they flow down the axonal pathways to infect the tissues they supply. Recurrent lesions are usually mild and less responsive to antiviral therapy.

Herpes labialis or "cold sores" is a lesion of multiple blisters at the border of the lip which ruptures, scabs and heals without scarring. The condition can be prevented or altered by the application of antiviral cream at the onset of the prodromal symptoms. However, immediate lesions are not preceded by any symptoms and appear all of a sudden. These lesions are associated with viral dormancy in the epithelial cells rather than in the neural tissue. In case of immune suppression, antiviral cream may not be enough and a systemic antiviral agent may be required (Table 5.7). Systemic antiviral therapy may be used as a prophylaxis in case of surgeries involving the ganglia or facial peel procedures to avoid outbreaks of the virus. Chronic suppressive therapy to prevent viral infections in those with more than six recurrences annually or in cases associated with erythema multiforme is also indicated.

Table 5.7: Selection and regimen of antiviral for recurrent herpetic lesions

Lesion form	*Agent and dose*
Simple form in healthy patient	Self-limiting disease Topical acyclovir 5%/5/day Topical penciclovir 1%
Defective immunity	Acyclovir 400 mg/5 times till healing
Chronic suppression	Acyclovir 400 mg/bid/1y Valacyclovir 1 g/OD/1y Famciclovir 250 mg/bid/1y

Recurrent intraoral herpetic lesions involve mainly sites of trauma like the attached gingiva and the palatal mucosa. Recurrent lesions involve only one surface, in contrast to primary one, and is often less severe. In its early stages, acyclovir, valacyclovir, famciclovir or foscarnet may help in its prevention or modification.

The diagnosis of herpes simplex lesions is based on clinical appearance and is often straightforward. The diagnosis may need to be confirmed sometimes and the use of Tzanck test may show multinucleated epithelial giant cells which are virally-infected. Other tests include viral culture and immunofluorescence, but these need to be carried out in the hospital environment.

Varicella. Chickenpox, a childhood disease caused by HZV, gains its access through the mucous membranes of the upper respiratory tract. It gets distributed by blood (viremia) to other tissues. The lesions start by the production of macules, papules and later the clear drop vesicles which soon rupture and scab. The infection is self-limiting in healthy individuals, but may be life-threatening in patients with defective immunity (risk of fulminating varicella pneumonia). Passive immunization may be indicated for those who are pregnant to prevent effects on the developing fetus (Table 5.8).

Shingles. Like HSV, HZV remains in chronic infection state at the dorsal root ganglia, commonly of the L1, L2, C3, T5, and sensory branches of the trigeminal nerve. Depressed immunity, trauma and elderly all act by triggering its activation. Areas supplied by the affected ganglia are seen with prodromal pain, being burning, or in some cases neuralgic in nature. Vesicles later develop and follow the same course as the primary infection except for that secondary bacterial infections are common which may result in scarring. This condition may be followed by another painful condition known as post-herpetic neuralgia (PHN) which is more prevalent in elderly. Systemic antiviral therapy is indicated in case of severe involvement, in those with depressed immunity and in elderly (Table 5.8). The associated pain may be difficult to manage with the usual analgesics and the following were tried:

Table 5.8: Selection and regimen of antiviral for HZV infections

Associated lesions	*Agent and dose*
Varicella	
Healthy	Self-limiting, only supportive measures and infection precautions
Depressed immunity/ severe cases	Acyclovir (IV) 15–30 mg/kg/day for 7 days
Shingles	
Healthy	Topical acyclovir 5% and antiseptic mouthwash
Depressed immunity/ severe cases	Acyclovir 800 mg/5t/10 days Valacyclovir 1 g/tid/10 days Famciclovir 500 mg/tid/10 days
Elderly	Same as severe cases plus prednisone 40–60 mg/day/3 weeks†

† Prophylactic against PHN, decreased gradually.

adjuvant analgesics (as tricyclic antidepressants, carbamazepine), physical stimulation (like massaging or applying firm pressure), or thermal application (in the form of local heat or cold spray). Prednisone may help in pain relief and healing enhancement.

Glandular fever. Also known as infectious mononucleosis, glandular fever is caused mainly by EBV. However, other viruses like CMV or HHV6 may be involved. The disease is characterized by rashes and jaundice in the febrile type, exudates on the fauces with sore throat and edema in the anginose type and lymph node enlargement with splenomegaly in the glandular type. The disease is associated with the production of autoantibodies with agglutination effects on sheep or horse RBCs (Paul Bunnell test). The disease is self-limiting and requires no treatment other than supportive measures. Pharyngeal edema may necessitate the use of steroids to guard against air way obstruction. It should be noted that administration of amoxicillin may produce a nonallergic skin rashes on the extremities. No antiviral is required as they show no effects on the symptoms or the virally-infected cells.

Caused by Coxsackie viruses, *herpangina* and *hand-foot-mouth* disease are more common in children. Because their treatment needs only supportive measure and needs no antiviral therapy, they should be differentiated from other lesions like AHGS or HZV infections.

Mumps is an acute inflammation of major salivary glands, most commonly being the parotid. It should be differentiated from bacterial sialadenitis, buccal space infection and lymphadenitis. Serum test for S and V antibodies is positive. The condition, however, does not need antiviral therapy and only symptomatic treatment is indicated. In children, aspirin should be avoided to prevent fulmination of the disease (Reye's syndrome).

GENERAL CONSIDERATIONS

Most viral infections are self-limiting, but some may require the use of antiviral therapy. Antiviral drugs may help in decreasing pain and the time needed for healing. Because viral replication occurs before the manifestations start to appear, it would be difficult to prevent viral infections. Early use of antiviral agents would provide better results than when used late. It should be remembered that the antiviral therapy does not affect the viral in its dormant state and periods of recurrence are expected. Infants, elderly and immunocompromised should be treated more aggressively.

The patient's nutritional state should be taken into consideration. The patient is instructed to increase fluid intake and to have high calorie diet. Pain should be managed to allow for rest and adequate nutrition. Secondary bacterial infections should be prevented by the use of antiseptic mouthwash. The patient should be informed of the infectious nature of the lesions to avoid infection spread to other sites like the conjunctiva or other family members.

Table 5.9: Showing specific considerations regarding antiviral use

	Pregnancy
Use	*Avoid*
Acyclovir cream	Acyclovir*
Penciclovir cream	Valacyclovir
	Ganciclovir
	Famciclovir
	Breastfeeding
Use	
Acyclovir Ganciclovir†	
Renal disease	
Dose adjustment‡	**Avoid (Nephrotoxic)**
Acyclovir	**Foscarnet sodium**
Valacyclovir	**Cidofovir**

* Can be used in serious cases where its benefits are justified over its effects.

† Rifampicin can be used as a replacement.

‡ Drugs accumulate in the body with possible toxicity.

SPECIFIC CONSIDERATIONS

Regarding pregnancy, most antiviral agents are harmful and should be avoided. However, topical forms are associated with lesser effects and hence considered safer. In sever cases, it might be justified to use systemic agents, like acyclovir, however.

The urinary system is involved in the process of antiviral elimination. Therefore, it is expected that patients with renal disorders might suffer toxicity if an antiviral is used in the normal doses. Consultation regarding the dose and choice of antiviral agents should be made in case of renal disease. Table 5.9 summarizes the specific considerations regarding antiviral use.

Box 5.2: Drug interaction

Acyclovir appears to reduce the level of valproic acid or phenytoin. On the other hand, it may be associated with theophylline toxicity. Theophylline toxicity has also been associated with concurrent use of **interferon**, recombinant protein which inhibits the hepatic microsomal system. Other drugs metabolized in the liver are also at risk of toxicity. As with penicillin, the use of probenecid also elevates the level of acyclovir or **valacyclovir**.

Because of their nephrotoxic effects, **acyclovir**, **valacyclovir**, **ganciclovir** or **cidofovir** should not be used with nephrotoxic agents.

Zidovudine, agent used in the management of AIDs, is known for its nephrotoxicity and bone marrow suppression. It may result in lethargy when used with acyclovir, and severe bone marrow depression along with blood dyscrasias if used with ganciclovir.

Interferon is known for its inhibitory effects on the hepatic enzymes. Accordingly, drugs metabolized in the liver may accumulate in the body and cause toxicity. In addition, interferon used with zidovudine potentiates the myelosuppression effects.

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Chapter 6

Emergency Drugs Used in Dentistry

INTRODUCTION

An emergency is an urgent situation with possible life-threatening outcome if no immediate medical care is provided. It reflects the inability of the body to maintain its internal environment constant (loss of homeostasis). This is why an external help is needed.

It is well known that emergency rates would be expected to be higher in elderly and immunocompromised individuals, as these patients respond unfavorably to stress. Long and extensive dental procedures are also potential factors.

PREVENTION

Even if an emergency situation is managed successfully, the 100 percent success remains its prevention. Although it occurs all of a sudden, an emergency can be expected. It appears that most medical

emergencies occurring in the dental clinic are related to stress. Stressful situation can be caused by inadequate pain control, fear, long or extensive procedures, as seen in endodontic procedures or oral surgeries. Therefore, stress reduction by pharmacological or nonpharmacological procedures is the first line defense against emergencies. Sedation is one of the options available to reduce anxiety and stress and should be used in those who appear unmanageable by the gentle handling approach. The risk of respiratory depression and sedative overdose are possible emergencies associated with the use of sedatives and the dental team should be able to manage such situations.

Although every patient is a suspect of at least a simple emergency, some are at great risks. This would include those with CVD like AP; those on chronic drug therapy and of course those with positive history of allergy. A medical consultation, regarding a medically complex patient, is recommended even if the dentist is sure about his precautions. Referral to a physician is surely prudent in case of suspension of undetectable diseases.

PREPAREDNESS

Preparedness literally means the condition of full readiness, and this is especially meant for military actions. If an emergency attacks in the dental clinic, it should be faced with an ordered and a well organized team (army) with a leader who shows no signs of surprise or lack of confidence. The team should have enough knowledge and equipment to manage an emergency successfully. There should be a plan which was discussed and practiced before. Every member of the team should be assigned a specific task to perform at every emergency situation (Box 6.1).

A thorough knowledge and practice in BLS for every member of the dental team is a must. CPR ensures adequate blood perfusion to the brain and this saves time till more advanced medical help arrives. Current certification, periodic refreshing and recertification are prerequisites for clinical work. The dentist or the leader, however, should have a certification in advanced cardiac life support (ACLS)

Box 6.1: Tasks assigned to the members of the dental team in case of an emergency	
Leader	Recognize and directly manage the condition
Assistant	Assist the leader
Nurse	• Prepare emergency drugs • Receive the ambulance down hall
Receptionist	• Make all phone calls to bring advanced support • Watch and indicate the time elapsed since drug administration and for vital signs rechecking • Record the details of the event

as well. The oral and maxillofacial surgeon should be equipped with a certification in advanced trauma life support and he usually leads the dental team.

The dental clinic should be prepared with the primary emergency drugs. In order not to do harm, the use of drugs, indications and contraindications should be revised thoroughly by the leader. Knowledge about the underlying pathophysiology of an emergency enables the clinician to use the proper drug. Emergency drugs should be labeled and preferably prestocked for easier access and more convenient use. The use of these drugs often requires special equipment and these should be ready as well (Table 6. 1).

The team should be able to perform various procedures like monitoring of the vital signs (blood pressure and pulse), venipuncture, parenteral injections and endotracheal intubation.

For advanced management, ambulance help with hospital emergency care may be required. Therefore, a valid phone number of an emergency department of the nearest hospital should be readily displayed.

EMERGENCY DRUGS

For efficient emergency management, it might be needed to apply the use of certain emergency drugs (Box 6.2). For maximum benefits, therapeutic uses and contraindications should be constantly revised. Otherwise, more harm can be produced than benefits.

Table 6.1: Necessary equipment for administration of emergency drugs in the dental clinic

Use	*Equipment*	*Description*
Oxygen administration	Mouth barriers	• Allows for safe mouth to mouth ventilation
	Pocket mask	• Provides mouth to mask ventilation with 50% oxygen • Useful for single rescuer
	Bag-valve mask	• Uses atmospheric or pure oxygen with positive pressure from the compressible bag • Useful in two- rescuer
Airway management	Suction units	• Aspirates excess fluid, help in foreign body retrieval • Preferable to be with separate power source
	Oropharyngeal airway Nasopharyngeal airway	Provide patent unimpeded path for air to reach the lungs
Injectable drugs	Needles	Gauge 18–21
	Syringes	5 or 10 ml
	Tourniquet	• Helps in locating veins for IV access • May also help in reduction of the venous return to the heart and in bleeding management

An emergency kit prepared with the suitable emergency drugs should be available. It is important that the kit does not contain too much items to avoid confusion of the user. Ideally, the basic items necessary for basic or initial management should be included. For more convenience, the agents should be in the preloaded form.

Oxygen

The basic requirement of every cell in the body in order to produce energy is oxygen. For oxygen to reach the body cells, three systems

Box 6.2: List of emergency drugs

Mandatory drugs
- Oxygen
- Epinephrine
- Glycerin trinitrate

Basic emergency drugs
- Anticonvulsants
- Corticosteroids
- Antihistamines
- Bronchodilators
- Analgesics
- Antihypoglycemics
- Respiratory stimulant

are involved. The respiratory system works by blood oxygenation through the process of ventilation. The heart pumps this oxygenated blood through the vascular system to reach the level of gas exchange which occurs at the capillary level. The central nervous system works by regulating both the respiratory and the cardiovascular systems. Therefore, for hypoxemia to occur, a defect of one or more of these should be present. Hypoxemia may cause irreversible neural damage if not reversed in less than four minutes. Therefore, oxygen should be used nearly for every emergency situation (Table 6.2), except for hyperventilation. In hyperventilation, the level of carbon dioxide is lowered due to excessive unnecessary ventilation. Carbon dioxide is important for the respiratory control mechanism and for vasodilatation of the cerebral blood vessels. This ensures adequate blood perfusion and oxygenation to the cerebral tissue. Depletion of carbon dioxide causes poor perfusion via loss of vasodilatation activity. Further, the hypothalamus may secrete hormones and neurotransmitters which may interfere with heart functions.

For efficient oxygenation, the systems involved in that process should be checked. The airway should be patent allowing alveolar ventilation. Life-saving cricothyroidotomy should be performed when required. The CVS and blood volume should be checked to

Table 6.2: Mandatory drugs, doses and routes of administration

Oxygen	Dose varies according to the technique of administration: • Mouth to mouth (17%) • Face mask (40–60%) • Bag-valve mask (75–95%)
Epinephrine* 0.5–1 mg (1:1000)	• IM into the tongue or the floor of the mouth. The deltoid muscle can be used • IV, but better to be reserved for cardiac arrest or severe conditions • SC, but has slow action
Nitroglycerin Angisid	0.5 mg sublingual tablet
Nitrolingual	0.4 mg spray

* Short duration, subsequent doses may be needed.

ensure adequate oxygen transport from the alveolar sacs to the cellular cytoplasm. Otherwise, oxygen supply will not produce the expected results.

Epinephrine

Epinephrine is the second most commonly used emergency drug. It is normally produced as a hormone by the adrenal medulla and as a neurotransmitter by the sympathetic system. It binds to the adrenergic receptors with the net result of preparing the body to withstand and survive extreme situations and stress. Adrenaline increases the cardiac output, by enhancing its contractility, via the β_1-adrenergic cardiac receptors. Peripheral vasoconstriction, via the α_1-adrenergic receptors, serves by elevating the blood pressure for better brain and heart perfusion. In these two organs, however, blood vessels dilate under the effect of adrenaline bound to β_2-receptors. This ensures sufficient blood perfusion for better performance.

Other useful effects of adrenaline include relaxation of bronchial smooth muscle, stabilization of mast cell granules, and

hyperglycemic effects. In case of hypoglycemia, epinephrine may be used to elevate blood glucose level. It acts by stimulating the alfa cells of the pancreas to secrete glucagon. Other hyperglycemic effects are produced by enhanced hepatic glycogenolysis and inhibited insulin secretion.

Adrenaline is useful in many emergency situations. This includes acute allergic reactions, asthmatic attacks, cardiac arrest and even in hypoglycemia.

Epinephrine, however, should not be used in patients with history of hypertension (risk of CVA or cardiac arrhythmia). The number of adrenaline receptors is increased in case of high levels of the thyroxin hormone (hyperthyroidism) producing amplified effects of adrenaline. If needed, hyperthyroid patients should be given minimal doses. Table 6.2 shows the doses and routes of administration of epinephrine.

Adrenaline is metabolized by the catechol O-methyl transferase enzyme (COMT) which is present in the GIT and the postsynaptic clefts. Therefore, the oral form is expected to be rapidly inactivated. Intraneural metabolism is achieved by the monoamine oxidase enzyme (MOA). That is why adrenaline is short acting and the vital signs should be rechecked every 10 minutes when used in an emergency situation as further administration may be needed.

Nitroglycerin

As the name implies, nitroglycerin is a compound of nitric or nitrous acid easter of glycerol. Nitroglycerin is volatile in nature and is able to produce vasodilatation which enhances blood flow and oxygenation. It also acts by relaxing the venous system which helps in reducing the preload on the myocardium. This also would reduce the amount of oxygen requirement. All these effects made nitroglycerin a valuable remedy in the management of ischemic cardiac attacks and in case of high blood pressure.

Nitroglycerin is used sublingually to provide relief from anginal attach, usually within 1 to 3 minutes. It can be supplied in the form of tablet or spray (Table 6.2).

PRIMARY DRUGS

Anticonvulsants

Convulsions or seizures are conditions of sudden, but temporary, loss of consciousness accompanied with abnormal body movements. Epileptic attacks are caused by abnormally increased electric activity of a zone of neural cells in the cerebral cortex. These cells exhibit abnormal firing potential which is reached before normal cells.

Usually, fits are self-terminated, and the interference with anticonvulsant may be needed only in prolonged cases (status epilepticus) or in conditions interfering with respiration. For efficient control, the cause of the attack should be determined. Seizures can be idiopathic or produced secondarily to hyperventilation, hypoglycemia, syncope or thyroid storm.

Benzodiazepines (diazepam and **lorazepam)** are the agents used to end seizures (Table 6.3). They act on the GABAA receptors which would interfere with the cerebral neurotransmission. The most significant side effect of benzodiazepines is respiratory depression and prolonged sedation. **Flumazenil**, a benzodiazepine antagonist, may be required to reverse these side effects. It works by competitive inhibition and has more affinity to the GABA receptors than the benzodiazepines. However, the duration of action is short and frequent administration may be needed.

Care should be taken in patients' dependant on benzodiazepine therapy or those on tricyclic antidepressant medication as they are prone to seizures when flumazenil is provided.

Table 6.3: Anticonvulsants and sedative antagonists

Agent	*Route*	*Dose*
Diazepam		
Valium	IV, IM	5–10 ml
Valpam		
Lorazepam*	IV, IM	4 mg
Flumazenil†	IV only	100 mg/ml
Anexate		

* Short acting benzodiazepine.

† Benzodiazepine antagonist.

Corticosteroids (Table 6.4)

Physiologically, corticosteroids play an important role in the body. **Cortisol** from the adrenal cortex ensures normal performance despite stressful situations, like pain and disease. Cortisol receptors are found at every cell of the body. When secreted, cortisol acts by increasing glucose level for consumption and elevates the blood pressure for better organ perfusion and function. Patients with adrenal insufficiency or those dependants on long-term steroid therapy are at risk of cortisol shortage in case of stress or urgent situations. Instead of coping with stress, these patients may collapse.

Another function of cortisol is its potent anti-inflammatory/antiallergic effect which makes it the absolute option for acute inflammation and allergic conditions. It acts by dramatically decreasing the peripheral WBCs. It also interferes with the degranulation process of histamine-producing cells. In addition, PG, leukoterines and other inflammatory mediators are all blocked as it inhibits the phospholipas A enzyme, an enzyme responsible for the synthesis of arachidonic acid from membrane phospholipids.

Antihistamines

Histamine is a local inflammatory mediator which increases vascular permeability and causes edema. It is produced by degranulation of basophils or mast cells. These cells are sensitized by IgE which was previously produced in response to a similar antigenic stimulation. Once released, histamine acts on histamine receptors which are found at great numbers in the lungs, GIT and skin. Binding to H_1

Table 6.4: Corticosteroids

Agent	*Dose*	*Route*
Hydrocortisone **Solu cortef**	100–200 mg (100 mg/ml)	IV, IM
Dexamethasone† **Oradexon**	4 mg/ml	IV, IM

† Long acting corticosteroid.

Table 6.5: Antihistamines*

Agent	*% mg/ml*	*Dose (mg)*
Diphenylhydramine	10	20–50
Chlorpheniramine	10	10–20
Beadryl		
Pheniramine	22.5	45
Avil		

* All can be provided by IV or IM routes.

receptors, histamine mediates vascular permeability, smooth muscle contraction and mucus secretions. H_2 receptors, on the other hand, are present in the stomach and their activation facilitates gastric acid secretion.

Antihistamines bind competitively to histamine receptors but they don't inhibit histamine production. Their actions may take time, so, in some cases adrenaline may be used for more rapid relieve of allergy. Antihistamines are useful in mild or delayed allergic reactions (Table 6.5). Severe allergies would necessitate the use adrenaline and corticosteroids. Cortisone acts as an anti-allergic agent by blocking all the inflammatory mediators.

Antihistamines should not be used for acute asthmatic attacks as they may aggravate the condition by their drying effects.

Bronchodilators

β_2-agonists, like **albuterol**, are useful in managing conditions of bronchospasm and acute allergies. As stated for epinephrine, β_2-receptors are responsible for bronchodilation. These selective agents replaced theophylline which was associated with undesirable effects and drug interactions. They are present in spray form (Table 6.6).

Isoproterenol, however, is not selective and it acts on both β_1 and β_2. Therefore, more side effects are to be expected on the heart. Such effect can be useful, like adrenaline, in case of cardiac emergencies.

Analgesics

Analgesia may be required in certain painful medical conditions like MI. Due to severe pain and anxiety, the oxygen demand and

Table 6.6: Bronchodilators

Agent	*Dose and route*
Albuterol Ventolin Salbutamol Vental	0.1 mg/spray with two sprays considered sufficient

work load are increased, which may aggravate the ischemic heart attack. By rapid pain relief and anxiety control, the load over the heart will be reduced, as well as, its oxygen requirements.

Strong opioids like **morphine sulfate** or **meperidine** (Table 6.7), act on the opioid receptors with the result of intense pain relief. Care should be practiced, however, in case of brain damage or asthmatic patients as these analgesics induce respiratory depression and cause histamine release. Morphine sulfate has a useful effect other than being a strong analgesic as it acts by relieving pulmonary edema.

Naloxone narcotic antagonist may be needed to reverse unwanted effects like respiratory depression or unwanted sedation (Table 6.7). It works by displacing opioid from their receptors. Naloxone has about ten times more affinity to opioid receptors than morphine. Reversed sedation is expected in 30 seconds.

Nitrous oxide is also a potent analgesic which works also by bronchodilation and enhanced perfusion to the brain. However, muscle relaxation may affect the rate of respiration, an effect which deserves special attention.

ASA, although not used for the purpose of analgesia, is of benefit in case of MI. It secondarily affects platelet aggregation via blocking the thromboxane A_2 enzyme. This antiplatelet effect reduces the chances of death in patients having an IM as the risk of thrombus formation is lowered.

Antihypoglycemic Agents

Hypoglycemia may be caused by starvation or by relatively higher insulin dose in diabetics. Stress, exercise or insufficient food intake may disturb the balance between blood glucose level and insulin. As a result, fainting, convulsion and in severe cases, brain damage and

Table 6.7: Analgesics necessary for management of emergencies

Agent	*Dose*	*Route*
Morphine sulfate	10 mg	Oral
(10 mg/mL)	5 mg	IM
	2 mg	IV
Meperidine (50 mg/ml)	50 mg/ml	SC
Pethedine		
Naloxone* (0.4/ml)	0.4-2 mg	IV, SC
Narcan		
Nitrous oxide gas	35% with	Inhalation
	65% oxygen	
ASA† Aspocid	75–325 mg	Oral

* Narcotic antagonist.

† Non-enteric coated, chew and swallow.

death may the results. Brain cells depend on glucose for their metabolism and there is no glucose storage mechanism in their structure. In this case, antihypoglycemics may be life-saving.

The conscious patient can be supplied with **sugar tablets** or **soft drink** (Table 6.8). **Dextrose IV** in 50 percent concentration is indicated in case of hypoglycemia in unconscious patients. **Glucagon** can be used instead of dextrose when the latter is not present or when it is difficult to obtain venous access. Glucagon is an alfa cell pancreatic hormone which acts by elevating the blood glucose level by enhancing hepatic glycogenolysis and gluconeogenesis. **Epinephrine** is another hormone which elevates blood glucose level. It, too, acts by enhancement of glycogenolysis, induction of glucagon secretion and inhibition of insulin production.

Table 6.8: Antihypoglycemic agents

Agent	*Form and dose*
Sugar	Glucose tablets 3 g with vitamin C 150 mg
	Chocolate bar or soft drinks
Dextrose	50%, 50 ml IV
Glucagon	1 mg IM or SC
Epinephrine (1:1000)	0.5 ml SC

Table 6.9: Respiratory stimulant

Agent	*Dose and route*
Aromatic ammonia	0.3–0.4 ml, inhalation

Respiratory Stimulants

Aromatic ammonia is used as a respiratory stimulant and to awaken patients who are in syncope, due to its irritating properties to the mucous membrane (Table 6.9). Thus, the respiratory and the vasomotor centers in the medulla are stimulated. Both respiratory rate and blood pressure are elevated which help in regaining consciousness. For the fainted patients, aromatic ammonia may be the only required drug. In asthmatic patients, aromatic ammonia may precipitate an asthmatic attack, so its use is not recommended.

MANAGEMENT OF EMERGENCIES

In the following section, a brief description of some common medical emergencies that may occur in the dental clinic is provided in the form of Tables 6.10 to 6.18. The purpose of this section is to introduce these emergencies, delineate the clinical appearance, cause and pathophysiology and the proper management.

Table 6.10: Syncope (fainting, vasovagal attack)

Definition and clinical features	• Fainting or losing consciousness • Characterized by weakness, pallor, sweating, and loss of consciousness • If severe or prolonged, it might progress into a seizure
Pathophysiology	• Related to stress and anxiety or extreme fear. Hypoglycemia can be another factor • This causes overstimulation of the vagal system which decreases the cardiac output and blood pressure resulting in cerebral hypoxia

Contd...

Contd...

Management	• Lie the patient down into a flat position with legs elevated • Manage airway and administer oxygen • Monitor vital signs • Loosen clothes to enhance breathing and apply cold on the forehead. Cooling causes vasoconstriction which enhances blood return • The condition usually resolves in 2 minutes as the sympathetic system is activated • Aromatic ammonia may be used for prolonged fainting or with slow breathing • If the patient does not wake up, consider other causes of fainting and prepare for hospital transfer

Table 6.11: Acute asthmatic attack

Definition	Paroxysmal allergic condition associated with attacks of dyspnea
Clinical features	• Dyspnea, expiratory wheezing sound and cyanosis • Anxiety and apprehension aggravate the condition and loss of consciousness may occur
Pathophysiology	Allergic reaction to drugs (penicillin for example) or foreign material (like latex) causes bronchospasm, increased mucus production as well as edema of the mucous membrane. The condition can be stress-related
Management	• Reassurance to minimize stress • Place in erect position to enhance breathing • Give up to 4 metered doses of bronchodilator • Supply with oxygen to prevent hypoxia • Status asthmaticus (prolonged attack) may need the following: – IV sulbutamol (250 microgram) or 0.3 ml epinephrine SC – IV steroids – Transfer to hospital

Table 6.12: Hyperventilation

Definition and clinical features	• Abnormally increased respiratory rate, but with decreased depth of respiration • Characterized by dyspnea with shallow but rapid breaths • Fainting, perioral paresthesia, tremors, tetany (carpopedal spasm) and stomach pain with vomiting • Cardiac manifestations may occur and tachycardia, palpitation and chest pain may be seen • The patient may lose consciousness
Pathophysiology	• Anxiety, pain or fear causes tachypnea with increased carbon dioxide elimination. This would create metabolic imbalance (respiratory alkalosis) • The firing potential of muscle fibers and nerve cells is lowered and the tissues become hyper-excitable and possibly self-excited
Management	• Oxygen is contraindicated • Try to decrease the respiratory rate by reassurance and anxiety reduction • Increase the carbon dioxide content by re-breathing the exhaled air through paper bag or clubbed hands • If needed, provide nitrous oxide or midazolam 2–4 mg IM to control anxiety

Table 6.13: Epilepsy

Definition	Brain disorder associated with excessive electrical activity in a certain focus in the cerebral cortex
Clinical features	Characterized by sudden loss of consciousness with body rigidity, respiratory apnea and cyanosis at the tonic phase. The clonic phase is characterized by involuntary jerky movements

Contd...

Contd...

Pathophysiology	Stimulus like pain, stress, hypoxia* or infection may trigger the zone of abnormal cells to produce excessive electrical discharge
Management	• Protect the patient from injury and place in recovery position. This would allow for secretions to sweep out and prevent the interference of the tongue • Give oxygen and monitor the vital signs. Fits increase oxygen demand and compromise respiration, as well • If not recovered in 10 min (status epilepticus), give diazepam 10 mg IV or midazolam 5 mg IM and call for medical emergency

* Careful consideration when giving benzodiazepines, oxygen supplement is a wise decision.

Table 6.14: Acute anginal attack

Definition	Acute chest pain due to narrowed coronary artery
Clinical features	• Moderate to severe retrosternal compressing pain which is sometimes reported as "an elephant standing on the chest" • Pain may radiate to the left shoulder or arm or left side of the lower jaw • Pulse is regular, and if not it might be an MI • It differs from indigestion in that the patient does not feel hungry and not on antacid therapy
Pathophysiology	Increased oxygen demand due to stress or anxiety with atheroma narrowing the coronary artery exposes the myocardium to ischemic attack and this causes pain
Management	• Reassure, enhance ventilation and decrease venous return by erect position • Sublingual nitroglycerin tablet (0.5 mg) or spray • Give oxygen • Check vital signs, if pulse is irregular treat as MI • If not resolved in 5 min, give another tablet of glycerin trinitrite • After 3 doses, if pain continues, manage as MI

Table 6.15: Myocardial infarction

Definition and clinical features	• Similar to AP except for the irregularity in pulse and reduced blood pressure. However, the associated pain may be more severe and not resolved by the use of nitroglycerin • If not managed properly, the patient may lose consciousness or goes into cardiac arrest*
Pathophysiology	• The presence of atheroma in the coronary arteries may be big enough to cut off the blood supply to the myocardium • Ischemic attack is precipitated by stress or anxiety with increase heart oxygen requirement. Cellular necrosis or infarction results
Management	• If MI is not suspected, the condition is managed initially as AP • If pain is not resolved after 3 nitroglycerin tablets, or when MI is suspected due to irregular pulse or low BP then give: – Analgesia: morphine sulfate 10 mg or meperidien 50 mg IM. Nitrous oxide analgesia may be used (50/50) – ASA 300 mg to prevent thrombus formation • If cardiac arrest ensues, start CPR and monitor vital signs till advanced help arrives

* Silent form of MI may occur in diabetic patients where no chest pain is felt. However, shortness of breaths, sense of impeding doome and general feeling of weakness may be the reported symptoms. MI is a common cause of cardiac arrest.

Table 6.16: Cardiac arrest

Definition	It is a life-ending condition where the heart stops its function
Clinical features	• Unconsciousness, where the patient is unresponsive • Absent pulse in the carotid or femoral arteries • Grasping breaths or breathing may be absent • Cyanosis and pupil dilatation
Pathophysiology	• The heart function may be arrested by MI, drug toxicity, severe hemorrhage or acute hypotension (e.g., due to adrenal crisis or anaphylactic reaction) • Oxygen supply to the body cells is cut off with their metabolic wastes not removed resulting in anoxia and metabolic acidosis, respectively
Management	• Transport the patient to a firm flat surface and start CPR: – Establish patent air way, provide source of ventilation (mouth to mouth or ambu bag) – Apply external chest compressions in the rate of 60 to 80/minute and depth of 5 cm. Monitor for the vital signs periodically. Elevate the legs to enhance venous return • Provide adrenaline injection IV or IM • Call for medical assistance • Signs of response are spontaneous pulse and breathing, reflex activity and pupil constriction • If nonresponsive in 15 min, the patient is probably dead

Table 6.17: Hypoglycemia

Definition	A condition of reduced blood glucose level usually due to imbalance between the hypoglycemic drug and calorie intake
Clinical features	Slurred speech, blurred vision, altered behavior, sweating, weakness tachycardia, anxiety, loss of consciousness and convulsions
Pathophysiology	• Normal insulin injection with missed meal, stress, anxiety or infection all increase the energy demand and, thus, exhaust the glucose available • Continued low glucose level leads to neural necrosis
Management	• Place in flat position • Conscious (recognizable early signs): provide oral glucose • Unconscious patient: – Glucose IV (50 ml/50% dextrose) over 2 to 3 minutes, Or – Glucagon 1 ml IM, Or – Epinephrine* 0.5 ml (1:1000) SC – Monitor vital signs and provide oxygen

Table 6.18: Anaphylactic reaction

Definition	Literally it means "lack of protection", a condition of severe immediate hypersensitivity reaction
Clinical features	• Cutaneous: Including erythemia, urticaria and angioedema • Respiratory: Dyspnea and wheezing sounds followed by cyanosis • GIT and urinary: Vomiting and urinary incontinence • Circulatory: Hypotension, tachycardia, cardiac dysrythmia or even cardiac arrest
Pathophysiology	• Allergen (usually in the IV form) combines with the already formed IgE* creating antigen-

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	antibody complexes which, in turn, cause degranulation of mast cells. Histamine and other inflammatory mediators are librated in massive amounts • This leads to vasodilatation, increased vascular permeability and hypotension • Bronchospasm and laryngoedema cause dyspnea or even apnea
Management	• Enhance venous return by placing in supine position • 0.5 mg epinephrine (1:1000) IV or IM (it acts by increasing cardiac output, blood pressure, bronchodilation and stabilization of mast cells). Check the effects of epinephrine every 5 minutes. Give other injections if needed • Provide basic life support (CPR): – Airway (A): Establish patent airway and if needed cricothyroidotomy or tracheotomy may be performed – Breathing (B): Provide oxygen – Circulation (C): Chest compressions in case of cardiac arrest • 100 to 200 mg hydrocortisone IV (to maintain blood pressure and for absolute anti-allergic action) • 50 mg diphenylhydramine or 10 mg chlorpheniramine (antihistamine) IV or IM • Monitor vital signs periodically till advanced medical support arrives

* IgE is found at higher concentrations at the adenoids, tonsils, bronchi, GIT and urinary bladder.

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