PHARMACOLOGY

STUDENT BOOK SENIOR 5
ASSOCIATE NURSING PROGRAM

First Edition

FOREWORD

Dear Student

The Rwanda Basic Education Board is pleased to introduce this textbook of Pharmacology of the Associate Nursing Program. This resource is crafted to support competence-based teaching and learning, ensuring a uniform approach to mastering the Pharmacology. Our educational philosophy is designed to help you realize your full potential at each level of your education, equipping you to integrate effectively into society and seize career opportunities.

The Rwandan government emphasizes the alignment of educational materials with the syllabus to enhance your learning experience. Instructional materials, activities, and engagement play a crucial role in shaping how well you learn. This textbook focuses on activities that promote idea development and discovery, whether done individually or in groups.

In a competence-based curriculum, learning is an active process where knowledge, skills, and attitude and values are developed through practical activities and real-life scenarios. To fully benefit from this textbook, you should:

- Engage in activities and laboratory experiments to build your skills.
- Share information through presentations, discussions, and collaborative work.
- Take ownership of your learning and draw insights from your activities.

I extend my gratitude to all those who contributed to the creation of this book, including the Ministry of Health, University of Rwanda, and other institutions. Special thanks go to the dedicated faculty members, nurses, midwives, teachers, illustrators, and designers who worked diligently on this project.

Dr. MBARUSHIMANA Nelson

Director General, REB

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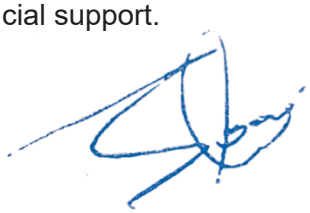

Ms. MURUNGI Joan

Head of Curriculum, Teaching, and Learning Resources Department / REB

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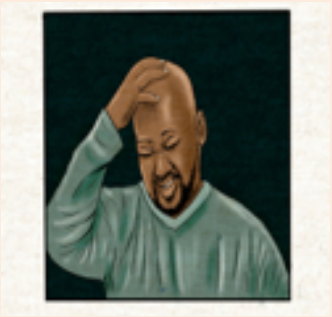
UNIT 1: MEDICATIONS FOR PAIN, FEVER, SEIZURES AND INFLAMATION

Key Unit competence:

Provide appropriate medications for pain, fever, inflammation, and seizures.

Introductory activity 1.0

A



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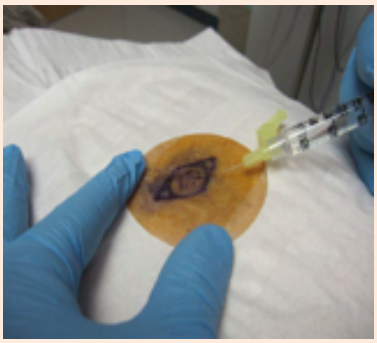


D

E

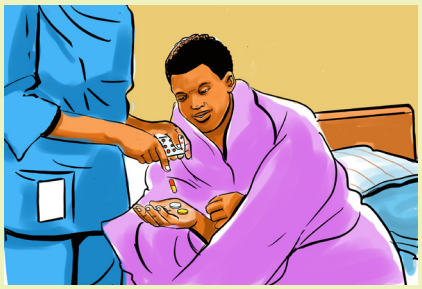
Observe the images above and respond to the following questions:

1. What do you observe from the images above?
2. What do you think people on the images above are doing or experiencing?

1.1. Overview on pathophysiology of fever

Learning Activity 1.1

1. Ill patients can express different symptoms in their illness status which are found during nursing assessement and managed with different medications

A **B** **C**

2. Patient on image A started complaining of health condition, and the assessment's data have shown a high fever of 38.5oc. different medications were selected for the management of the case (Image C & B). Using library textbooks, describe the physiology of fever.

CONTENT SUMMARY

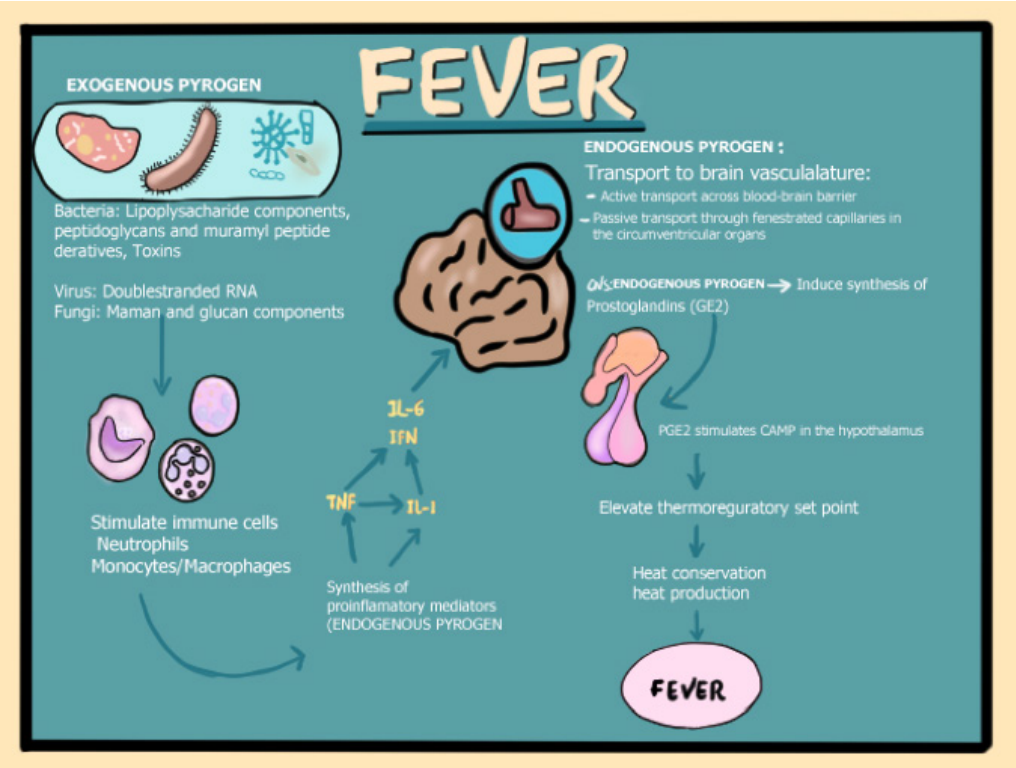
Thermoregulation is interceded by the hypothalamus. Peripheral thermoreceptors located in different body parts as skin, abdominal organs, as well as central thermoreceptors found in the spinal cord and other central locations offer the hypothalamus with information about skin and core temperatures. If these temperatures are abnormally high, the hypothalamus responds by triggering or heat loss mechanisms. While, when the temperatures are abnormally low the hypothalamus responds by triggering heat production, heat conservation.

Body temperature is determined by the balance between heat production by tissues, particularly the liver and muscles, and heat loss from the periphery. Normally, the hypothalamic thermoregulatory center maintains the internal temperature between 37° and 38° C. Fever results when something raises the hypothalamic set point, triggering vasoconstriction and shunting of blood from the periphery to decrease heat loss; sometimes shivering, which increases heat production, is induced. These processes continue until the temperature of the blood bathing the hypothalamus reaches the new set point. Resetting the hypothalamic set point downward for

example, when antipyretic drugs are given, initiates heat loss through sweating and vasodilation. The capacity to generate a fever is reduced in certain patients like alcoholics, the very old, the very young.

Pyrogens are substances that cause fever. Exogenous pyrogens are usually microbes or their products. The best studied are the lipopolysaccharides of gram-negative bacteria, commonly called endotoxins and *Staphylococcus aureus* toxin, which cause toxic shock syndrome. Fever is the result of exogenous pyrogens that induce release of endogenous pyrogens, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and IL-6 and other cytokines, which then trigger cytokine receptors, or of exogenous pyrogens that directly trigger Toll-like receptors. Prostaglandin E2 synthesis appears to play a critical role.

Fever is a natural defense mechanism for neutralizing foreigner organisms. High body temperature or fever destroys and kills many species of bacteria; but when it remain high it destroy even some normal cells of human body. Medications used to treat fever are known as antipyretics



Fever is diagnosed by measuring body temperature using thermomether , The use of thermometer to measure body temperature is the most accurate way of diagnosing fever. Sites for fever mesearument include oral,axillary,tympanic,anal depending on available materials, age, status and preferance of the patient.

A nurse should consider as fever the temperture above 37.5^{0}c, if the thermometer is not available touching the skin is an other alternative even though,it is less acurate and can expose to any other health related problems such as infection desease transmission. This is especially the case if you're self-diagnosing. When using touch to diagnose a fever in someone else, touch your own skin first, then touch the other person to compare the two temperatures. If the other person is a lot hotter than you, they may have a fever. You can also try pinching the skin on the back of your hand to check for signs of dehydration. If the skin doesn't snap back quickly, you might be dehydrated. Dehydration may be a sign of a fever.

Self assessment 1.1

Complete the following sentences:

1. When the body's temperature is very low, the hypothalamus responds by…….
2. When the body temperature is very high, the hypothalamus responds by …….

1.2 Medications for fever

Learning Activity 1.2

A 20 years old female patient went to the health facility because she was worried about the high fever, shivering, sweating. She was experiencing the symptoms since yesterday. After admission, they found that her axillary body temperature is 39.0oc, and directly she received two tablets that she swallowed immediately before other intervention that were proposed.

Using Library textbooks, respond to the following questions

1. What is an antipyretic drug?
2. Describe the mechanism of action of Paracetamol?
3. Identify the forms of Paracetamol?

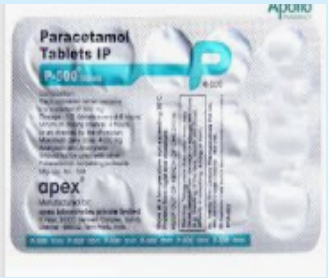
CONTENT SUMMARY

Fever is treated by different medications including **Acetaminophen** or Paracetamol which is a commonly used antipyretic. It is classified in antipyretic analgesic drugs**.** **Paracetamol** is a chief of group of medication used to reduce fever by direct action at the level of the hypothalamus and dilation of peripheral blood vessels, which enables sweating and dissipation of heat.

Acetaminophen has the equal efficacy to reduce fever as **ibuprofen**, and **aspirin,** however this aspirin and ibuprofen have anti-inflammatory properties that is why acetaminophen is used as the primary therapeutic usefulness for the treatment of fever in patients. Acetaminophen is rapidly engrossed from the gastrointestinal tract, attainment peak levels in 0.5 to 2 hours. It is extensively metabolized in the liver and excreted in the urine, with a half-life of about 2 hours.

Caution should be used in patients with hepatic or renal impairment could restrict with metabolism and excretion of the drug. Acetaminophen crosses the placenta and goes into breast milk; it should be used vigilantly during gestation or lactation because of its potential adverse effects on the fetus or neonate.

The dosage of paracetamol depends on age and the level of fever**.** In Adults and adolescents, 500mg to 1000 mg every 6 to 8 hours per day the maximum is 4000 mg in 24 hours. Whereas for paediatric clients it is 10-15 mg/kg 4-6hrly. Paracetamol is available in many forms. Acetaminophen is available as tablets, caplets, solutions, suppositories and injectable. It is a Pregnancy category B drug.





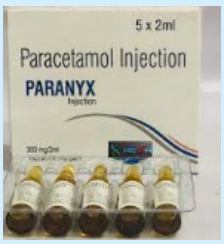



Figure1.1: Different forms of Acetaminophen

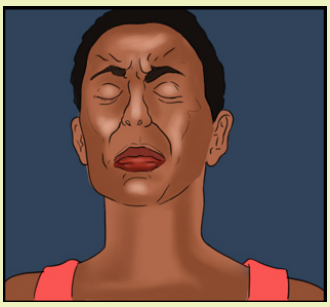
Adverse effects associated with acetaminophen use include headache, hemolytic anemia, renal dysfunction, skin rash, and fever. Hepatotoxicity is a potentially fatal adverse effects that is usually associated with chronic use and overdose and is related to direct toxic effects on the liver. The dose that could prove toxic varies with the age of the patient, other drugs that the patient might be taking, and the underlying hepatic function of that patient. When overdose occurs, acetylcysteine can be used as an antidote. Life support measures may also be necessary.

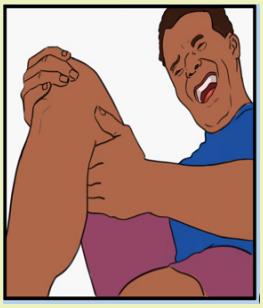
Self assessment 1.2

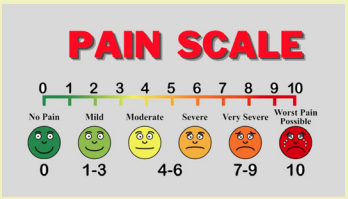
1. Identify at least 3 medications used to manage fever?
2. What is the correct dosage of paracetamol in children?
   A. 10mg/kg every 6hours
   B. 10mg to 15mg/kg
   C. 10mg to 20mg/kg
   D. 10mg to 15mg /kg every 4 to 6 hrs.
3. Choose all correct answers: The adverse effects of paracetamol are
   A. Headache,
   B. Kidney dysfunction
   C. Bleeding
   D. Skin rash
   E. Pruritis

1.3. Overview on pathophysiology of pain

Learning Activity 1.3







These patients above are expressing the same health problem at different sites. Use library textbooks and internet to respond to the following question.

a) What is pain?

b) How can the pain be assessed?

CONTENT SUMMARY

Pain is a displeasing sensory and emotional experience related to real or potential tissue impairment. It arises with many disorders, diagnostic tests, and treatments. It incapacitates and distresses more people than any single disease. It is the most common reason for consultation in health care facilities. Sensory experience of pain depends on the interaction between the nervous system and the environment. The processing of noxious stimuli and the resulting perception of pain implicate the peripheral and central nervous systems.

Among the nerve mechanisms and structures involved in the transmission of pain perceptions to and from the area of the brain that interprets pain are nociceptors, or pain receptors, and chemical mediators.

Nociceptors are receptors that are preferentially sensitive to a noxious stimulus. Nociceptors are also called pain receptors; Nociceptors are part of complex multidirectional pathways. These nerve fibers branch very near their origin in the skin and send fibers to local blood vessels, mast cells, hair follicles, and sweat glands. When these fibers are stimulated, histamine is released from the mast cells, causing vasodilation. Nociceptors answer to high-intensity mechanical, thermal, and chemical stimuli.

Some receptors respond to only one type of stimuli; others, called polymodal nociceptors, respond to all three sorts of stimuli. These highly specialized neurons transfer the mechanical, thermal, or chemical stimulus into electrical action or action potentials. The cutaneous fibers located more centrally further branch and

communicate with the paravertebral sympathetic chain of the nervous system and with large internal organs. As a result of the connections among these nerve fibers, pain is often accompanied by vasomotor, autonomic, and visceral effects. In a patient with severe acute pain, for example, gastrointestinal peristalsis may decrease or stop.

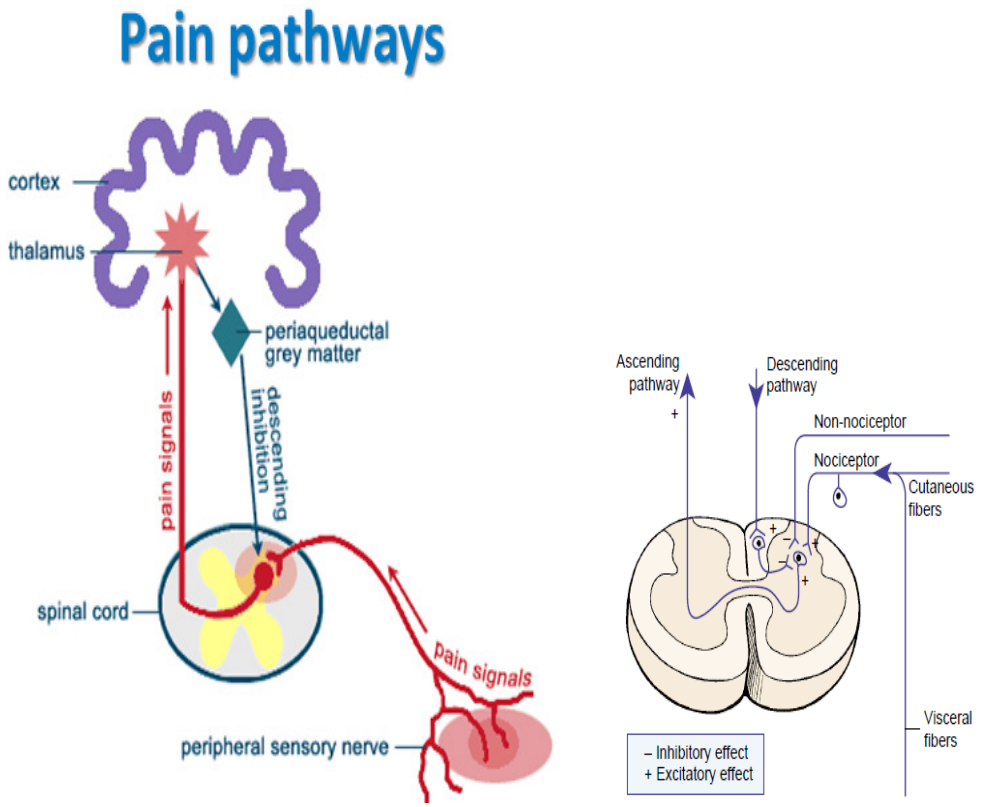


Figure 1.3.1: Pain pathway

Physiologically, pain occurs when sensory nerve endings called **nociceptors** (also referred to as pain receptors) come into contact with a painful or noxious stimulus. The resulting nerve impulse travels from the sensory nerve ending to the spinal cord, where the impulse is rapidly shunted to the brain via nerve tracts in the spinal cord and brainstem. The brain processes the pain sensation and quickly responds with a motor response in an attempt to cease the action causing the pain.

Pain can be caused by a mechanical, chemical or inflammatory, or thermal mechanism. Pain of *mechanical* origin can be caused by acute trauma, injury, or overuse. It may be constant, variable, or intermittent in nature and is affected by movement and position. Pain of *chemical* or *inflammatory* origin is associated with arthritis and other inflammatory disorders. It is often constant but responds to positioning, therapy, rest, and gentle movement. Pain of *thermal* origin is the result of excessive heat or cold.

If an acute pain sensation is intense enough, it can cause system-wide responses: increased alertness; focused attention; the suppression of feeding, sleep, and reproduction; and increased vascular tone, respiration, and blood sugar levels. If pain persists or becomes chronic it can even change the circuitry in the central nervous system. Medications are usually a part of the management regimen for chemical or inflammatory pain.

Table 1.3.1: Factors influencing pain perception

Factors influencing pain perception	
Physiologic/ biologic	– Site of injury or source of painful stimuli – Intensity of stimulation/degree of tissue damage. – Type and density of stimulation of receptors present – Biologically based individual differences in pain threshold and sensitivity
Psychological factors	– Emotional status of the individual – Individual beliefs and expectations regarding the experience of pain – People beliefs regarding their ability to establish control over the pain – The individual's history of pain experiences and pain sensations based on cultural and learning effects. – General physical health of the person with pain.

Factors influencing the pain response include past experiences to pain, anxiety, culture, age, gender, and expectations about pain relief. These factors may increase or decrease the person's perception of pain, upswing or reduced tolerance for pain, and affect the responses to pain.

Types of Pain

A. Nociceptive pain B. Neuropathic pain C. Sympathetic pain

Figure 1.3.2: Types of Pain

Types of **pain** include nociceptive pain or Physiological pain **(figure A)** which is a stimulation of sensory receptors for body and feels like aching, throbbing and sharp such us stubbing of toe or case of damage or disease. It can be Superficial when Skin and mucous membranes are involved, deep somatic when Muscles and joints are involved or visceral when Organs are involved.

Neuropathic pain **(figure B)** is an abnormal reaction to stimuli caused by damaged nerves. It can occur as a result of injury or infection. It can also flare up any time without an obvious pain inducing event or factor. It is mostly a burning pain. Sympathetic pain **(figure C)** is due to damage to sympathetic nerves. It is a burning pain with vasomotor instability and most of the time it is associated with regional sympathetic blocks.

The **pain assessment** begins by observing the patient carefully; noting the patient's overall posture and presence or absence of overt pain behaviors and asking the person to describe, in his or her own words, the specifics of the pain the words used to define the pain may ppoint toward the etiologic. The features to consider in a whole pain assessment are the intensity, timing, location, quality, personal meaning, aggravating and alleviating factors, and pain behaviors. **Pain is a subjective phenomenon.**

The highly subjective nature of pain Contests its assessment and management for every health care provider. The report of pain is a social deal; thus, assessment and management of pain require a good rapport with the person in hurt. In pain assessment, the health care provider reviews the patient's report of the pain and other factors that may impact pain as well as the person's response to pain liberation strategies. Documentation of the pain level as graded on a pain scale becomes part of the patient's medical record, as does a record of the pain relief obtained from interventions.

Pain assessment includes defining what level of pain relief the acutely ill patient, believes is needed to recover quickly or improve utility, or what level of relief the chronically or terminally ill patient requires to maintain wellbeing.

Many scales were designed to assess the extent of pain at different levels. The most commonly used scale is **numeric scale** that uses number to rate pain for people aged 9years and above.

By numerical scale, the patient rate verbally his/her client from 0 to 10 depending of his/her feeling of pain then the health care provider classify to no pain, mild pain, moderate pain, severe pain depending on the number the client has indicated and considering the figure below.

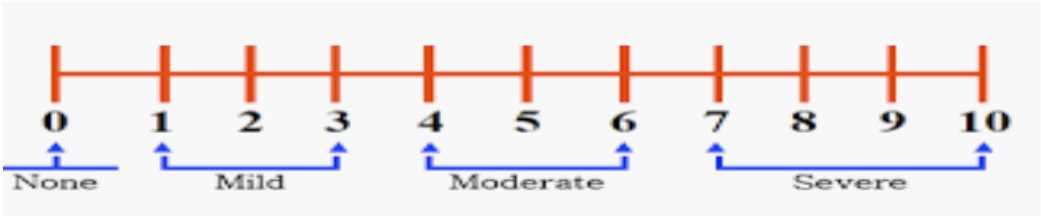


Figure 1.3.3: Numerical scale

Self assessment 1.3

1. Identify different types of pain?
2. Using a pain scale, a patient who scored 6/10 is considered having (which level of pain)?
3. Respond by True or false
   a. The pain is disagreeable sensory and emotional experience related only to diseases.
   b. The pain is subjective in nature.
   c. Pain medications always cause heavy sedation

1.4 Medication for pain management

Learning Activity 1.4

A patient was operated yesterday. He declares that the site of incision hurts very much. He did not sleep well the last night; he is crying in his bed.

Using library textbooks, respond to the following question

1. Identify classes of analgesics. Give an example for each class
2. What are the indications of morphine?
3. List the contraindication of tramadol

Analgesia is defined as insensibility of pain. Medications used to relive pain are analgesic or painkiller. Analgesics are classified as Opioid analgesics (strong opioid and weak opioid) and non-opioid analgesics that include salicylates (example aspirin), non-steroidal anti-inflammatory drugs like ibuprofen and acetaminophen. Strong opioid analgesic includes **morphine.**

It is indicated to relieve acute or chronic moderate to severe and to complement general, local, or regional anesthesia. It Binds with and activates opioid receptors

in brain and spinal cord to produce analgesia effect. Morphine has a half-life of 1.5 to 2 hours, metabolized in the liver, excreted in the urine and bile

All forms of morphine are contraindicated in case of asthma, hypersensitivity to morphine or its components, labor with premature delivery and respiratory depression or upper airway obstruction. Some side effects may arise when morphine is administered for example light-headedness, dizziness, sedation, Nausea, vomiting, dry mouth, constipation, ureteral spasm, respiratory depression, apnea, circulatory depression, respiratory arrest, shock, cardiac arrest. Morphine is available in various forms like capsules, Tablets, Oral Solution, Syrup, infusion.

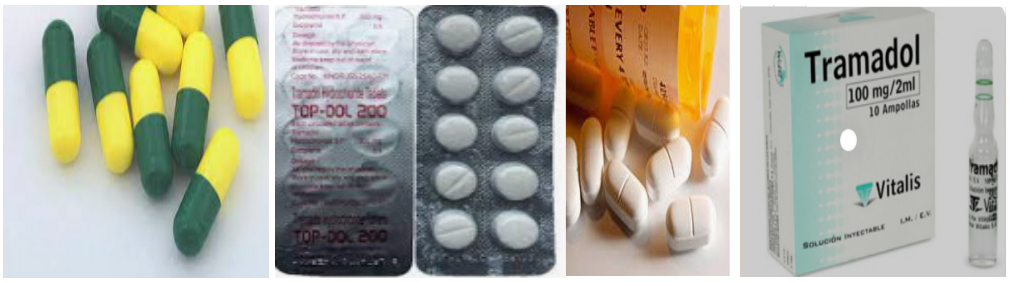
Figure 1.5: Forms of morphine

The dosage of morphine varies considering the form, intensity of pain, route of administration, indications and age of the patient. Tablets of morphine are administered as initial dose of 15 to 30 mg orally every 4 hours as needed to manage pain. For oral solution initial dose is 10 to 20 ml orally every 4 hours as needed. For maintenance dose individually titrate to a dose that provides an appropriate balance between pain management and opioid-related adverse reactions.

It is important to note that oral solution is available in 3 concentrations 2 mg/mL, 4 mg/mL, and 20 mg/mL; reserve use of 20 mg/mL concentration for patients who are opioid-tolerant. For the parenteral use, intravenous dosage is 0.1 mg to 0.2 mg/kg via slow IV injection every 4 hours, intramuscular administration is 10 mg IM every 4 hours alternatively, 2 to 10 mg IV as needed to manage pain (based on 70 kg adult). The dose of morphine is adjusted for pediatric patients .morphine is classified in pregnancy category c.

Tramadol is among the commonly used weak opioid. It is used to relieve moderate pain. It binds to the receptors and inhibits the reuptake of norepinephrine and serotonin this enhance tramadol analgesic effect. In adults and adolescents over age 16, it is administered 50 to 100 mg every 4 to 6 hr. as needed to manage pain without exceeding 400mg daily. It is reduced in hepatic and renal conditions. The maximum for patient aged 75 and above is reduced to 300 mg daily.

Tramadol should not be used for patient with history of addictions. Tramadol is contraindicated for persons with alcohol intoxication; excessive use of central-acting analgesics, hypnotics, opioids, or other psychotropic drugs; hypersensitivity to tramadol or its components. Tramadol is a pregnancy category C drug. Tramadol is available in different forms: capsules (a), tablet (b), caplets(c) and injectable(d).



a b c d

Figure 1.6: Forms of tramadol

Adjuvant drugs can be used to enhance the effects of pain medications, treat concurrent symptoms, and provide analgesia for other types of pain. Adjuvant analgesics are particularly useful when evidence of decreased opioid responsiveness is present.

Self assessment 1.4

1. Choose the correct answer:

Medications used to treat pain include:

A. Amoxicillin, paracetamol, tramadol
B. Paracetamol, morphine, erythromycin
C. Morphine, ibuprofen, diclofenac
D. Amoxicillin, Ibuprofen, tramadol

2. What are the contraindications for morphine administration?

A. Malaria
B. Asthma,
C. Respiratory depression
D. B and C

3. Which one among the following pain killers is a weak opioid?

A. Paracetamol
B. Tramadol
C. Aspirin
D. Ibuprofen

1.5 World health organization (WHO) pain management ladder

Learning Activity 1.5

Using library text books and internet search respond to the following questions, and note the findings

1. According to WHO Ladder, what are the levels of pain?
2. Explain how each level is managed?

CONTENT SUMMARY

The optimal pain control is multimodal and individualized. This does not contradict the value of the generalized WHO pain ladder, but clinicians should feel free to modify it, as needed, for individual patients, reflecting modern pain practice. The use of the pain ladder offers effective and cost-effective pain relief for patients suffering from chronic pain. The WHO pain ladder describes pain in terms of intensity and recommends that analgesics be prescribed starting at Step 1 using non opioid analgesics, such as acetaminophen or non-steroidal anti-inflammatory drugs such as ibuprofen If the pain persists or worsens, the clinician prescribes pain relievers from Step 2, described as **"weak opioids," such us tramadol** with or without a non-opioid. At this point, if pain persists or worsens, the patient is administered a "strong opioid," at Step 3. Thus, pain therapy is based on pain intensity and patients progress through the steps one by one, from lowest to highest, until pain relief is obtained.

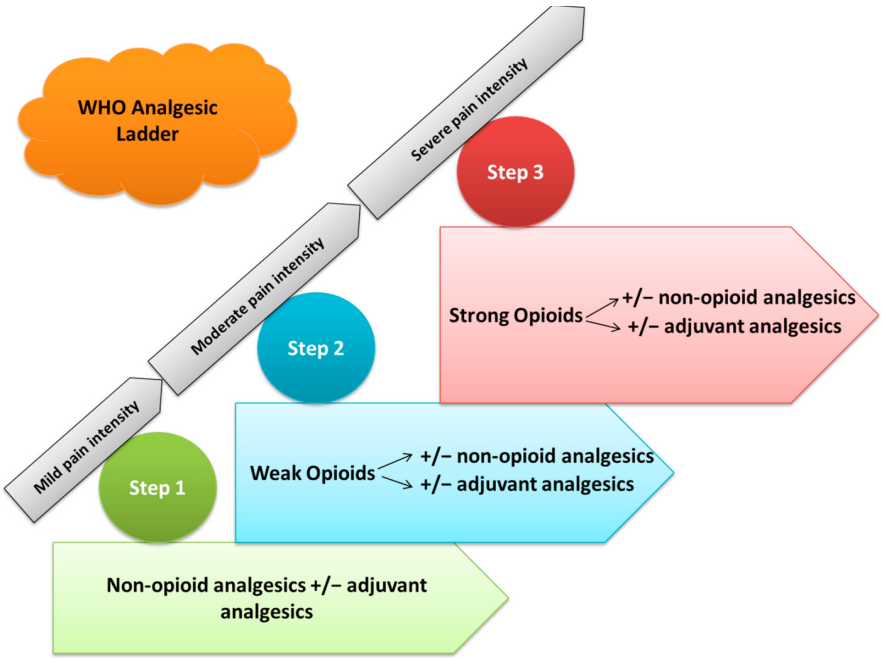


Figure 1.7: WHO Ladder

Reference: https://www.mdpi.com/1648-9144/55/9/584/htm

Myths about Pain

There are many barriers and **myths** regarding use of pain management medications and on overall pain management that can result in negative patient outcomes. Even if some myths are a part of the subculture of different medical disciplines, mistaken beliefs are universal throughout the healthcare system.

Some persons believe that the healthcare providers do an adequate job of providing adequate pain control. There is myth that pain medications always lead to addiction this belief prevent some clients and health care provider to use painkillers frequently.

There is belief that Pain medications always cause heavy sedation, some clients and professional refuse to administer prescribed dose thinking that there may be sedation. Again, there is belief that some kinds of pain cannot be relieved. These affect the client physically, emotionally when health care providers do not give painkillers thinking that the pain may not be relieved.

Pain and suffering are character-building. Same people assume that in same conditions of pain can empower the person with pain in personal resistance on different life challenges thought pain does not affect how the person pursue the external life challenges.

Narcotic analgesics in older patients should be avoided. This is not true, older person respond well on the effect of narcotic drugs if it has been administered with considerations for each patient specificity.

Self assessment 1.5

1. Which one among the following pain killers is a weak opioid?
   A. Paracetamol
   B. Tramadol
   C. Aspirin
   D. Ibuprofen
2. Which drug combination is true about the management of moderate pain according to WHO pain management ladder?
   A. Paracetamol +Buscopan
   B. Tramadol+ Buscopan
   C. Morphine+ Paracetamol
   D. Ibuprofen + Paracetamo
3. Why do we need to use adjuvant with painkillers in pain management?

1.6. Anaesthetics

Learning Activity 1.6

Read the following case study and respond to the questions asked at the end.

Mr N.A was running on the road as usual sport as he used to do in the morning, accidentally he falls down and a piece of glass severely cut him on the forearm. A s you were around you approached him and advise him to directly to the health facility, arriving there, the nurse said that Mr NA will need to be sutured. You heard that she will give an injection of anaesthetics of the site of injury before suturing.

Using library textbooks, respond to the following questions

1. What is an anaesthetic drug?
2. Why is it important to provide anaesthetic before suturing a wound?
3. Enumerate categories of anaesthetics?

Anesthetic is a drug used to cause complete or partial loss of sensation. It is called local anesthesia when it blocks nerve preventing depolarization of nerve membranes, blocking the transmission of pain stimuli and, in some cases, motor activity and it is general when it causes induction of loss of consciousness, amnesia (loss of memory), analgesia and loss of reflexes to allow surgical procedure performance. Induction is the time from the beginning of anesthesia until achievement of surgical anesthesia. Use of anesthetic agents suspends the sensation in parts of the body they exist.

The anesthetics can be subdivided into general and local anesthetics, depending on their site of action. General anesthetics are central nervous system (CNS) depressants used to produce loss of pain sensation and consciousness. Sedatives are agents given prior to induction of an anesthetic agent if indicated it leads on loss of conscious and muscle relaxation to easier other procedures such us intubation. Typically, the experience is smooth one and the patient has no recall of the events.

3 Stages of sedation

a) **Minimal Sedation,** the minimal sedation level is a drug-induced state during which the patient can respond normally to verbal commands. Cognitive function and coordination may be impaired, but respiratory and cardiovascular functions are not affected.

b) **Moderate sedation** is a form of anesthesia that may be produced intravenously. It is defined as a depressed level of consciousness that does not impair the patient's ability to maintain a patent airway. And to respond appropriately to physical stimulation and verbal command.

c) **Deep Sedation** is a drug-induced state during which a patient cannot be easily aroused but can respond purposefully after repeated stimulation The difference between deep sedation and anesthesia is that the anesthetized patient is not arousal. Deep sedation and anesthesia are achieved when an anesthetic agent is inhaled or administered intravenously.

Local anesthesia is the injection or application of a solution containing the local anesthetic into/to the tissues at the planned incision site. Often it is combined with a local regional block by injecting the nerves immediately supplying the area. The advantages of local anesthesia are as follows:

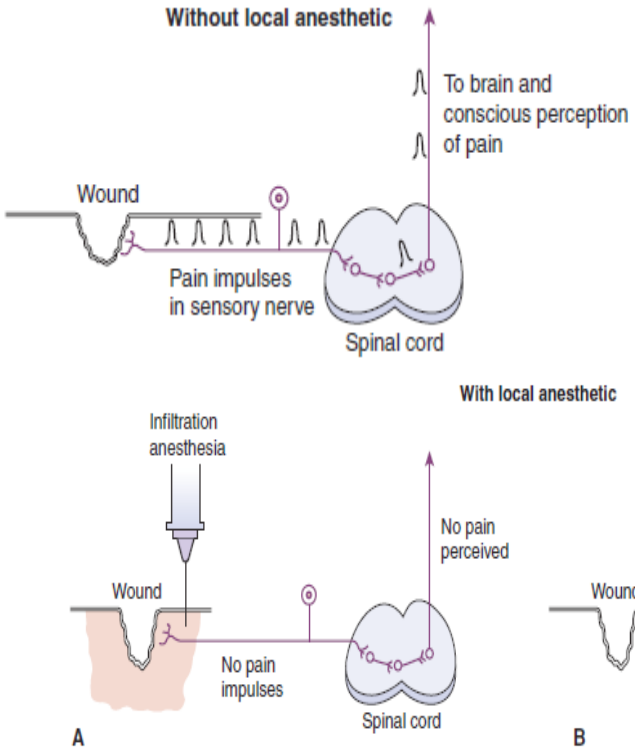
- It is simple, economical, and no expensive.
- Equipment needed is minimal.
- Postoperative recovery is brief.
- Undesirable effects of general anesthesia are avoided.
- It is ideal for short and superficial surgical procedures.

Local anesthesia is often administered in combination with epinephrine. Epinephrine constricts blood vessels, which prevents rapid absorption of the anesthetic agent and thus prolongs its local action. Rapid absorption of the anesthetic agent into the bloodstream, which could cause seizures, is also prevented. Local anesthesia is the anesthesia of choice in any surgical procedure in which it can be used.

However, contraindications include high preoperative levels of anxiety, because surgery with local anesthesia may increase anxiety. A patient who requests general anesthesia rarely does well under local anesthesia. For some surgical procedures, local anesthesia is impractical because of the number of injections and the amount of anesthetic that would be required. The skin is prepared as for any surgical procedure, and a small gauge needle is used to inject a modest amount of the anesthetic into the skin layers.

This produces blanching or a wheal. Additional anesthetic is then injected in the skin until an area the length of the proposed incision is anesthetized. A larger, longer Needle then is used to infiltrate deeper tissues with the anesthetic. Local anaesthetics include various classes like esters examples procaine, benzocaine, cloroprocaine, procaine, tetracaine and amides class where we find buvicaine, lidocaine, and mepivacaine. Local anesthetics block the depolarization of nerve membranes, preventing the transmission of pain sensations and motor stimuli (Figure B)

Local anesthetics are administered to deliver the drug directly to the desired area and to prevent systemic absorption, which could lead to serious interruption of nerve impulses and response



A: pain impulses status **B:** No pain impulses

Figure 1.6.1: pain impulse transmission

Local anesthetics

Bupivacaine (marcaine), etidocaine (duranest) those anesthetics are administered by infiltration peripheral nerve block the duration is 2–3 times longer it is used cautiously in patients with known drug allergies or sensitivities. While using bupivacaine should consider a period of analgesia persists after return of sensation; therefore, need for strong analgesics.

Procaine (novocaine) is administered subcutaneously, intramuscularly, intravenously, or spinal.it has low toxicity; inexpensive it can cause some idiosyncrasies skin rash poor stability. There is a need to observe for reaction such us hypotension, bradycardia, weak pulse. Usually administered with epinephrine, causing vasoconstriction, thereby slowing absorption and prolonging nerve deadening effect

Tetracaine (pontocaine) is administered to topical infiltration nerve block it causes topical infiltration nerve block but can cause some idiosyncrasies skin rash poor stability, as potent as procaine usually administered with epinephrine.

Lidocaine (xylocaine) and mepivacaine (carbocaine); Lidocaine can be administered in topical or injection**,** it is Rapid Longer duration of action, while

administer Lidocaine they should consider, Useful topically for cystoscopy Injected for use in dental work and surgery, Observe for untoward reaction, drowsiness, depressed respiration. Lidocaine is currently widely used local anaesthesia; it acts by blocking neuronal pain impulses. It may be injected as a nerve block for spinal and epidural anesthesia. It blocks sodium channels located within the membranes of neurons.

A B C

D E F

Figure1.6.2:Local Anesthetics

Lidocaine is available in injectable forms(*A*), Cream for topical use(*B*),spray (*C*) and patches (*D*). Their use will depend on the client, procedure to be performed and the desired effect. Solutions of lidocaine containing preservatives or epinephrine with vasoconstriction effect are intended for local anesthesia only and must never be given parenteral for dysrhythmias.

It is not advisable to apply topical lidocaine to large skin or broken areas as this lead to systemic absorption. It should not be in contact with eyes. Lidocaine is not indicated in case of hypersensitivity to amide local anesthetics. Application or injection of lidocaine anesthetic is also contraindicated in the presence of severe trauma or sepsis, dysrhythmias, sinus bradycardia, and severe degrees of heart block. Lidocaine is a pregnancy category B drug.

Local anaesthetics are generally very safe and serious problems are rare. However, some discomfort when the injection is given, a tingling sensation as the medication wears off, possibly some minor bruising, bleeding or soreness where the injection was given Some people experience experience temporary side effects from a local anesthetics, such as, dizziness, headaches, blurred vision, twitching muscles, continuing numbness, weakness or pins and needles. In very rare cases, you could have an allergic reaction to the local anesthetic or develop serious problems, such as seizures or a cardiac arrest. Precautions should be taken while injecting local anesthesia.

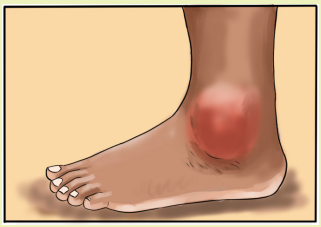
Self assessment 1.6

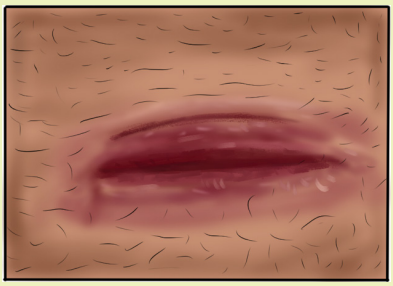
1. List at least 4 advantages of using local anesthetics
2. Identify at least 5 complications of local anesthetics
3. The following are the forms of Lidocaine except

   A. Tablets
   B. Sprays
   C. Injectable
   D. Cream

1.7. Overview on physiology of inflammation:

Learning Activity 1.7





1. What should be the problem on those images above ?
2. What are the causes of inflammation?(Please refer to library textbooks/ internet)
3. Explain the physiology of inflammation

CONTENT SUMMARY

In case the body get exposed to various stimuli like physical injury, exposure to toxic chemicals, extreme heat, invading microorganism or cell death, it reacts by defense mechanism called **inflammation.** The latter is considered nonspecific defense mechanism as it proceeds in the same way regardless of the cause that triggered it. The main purpose of infammation is to recover the body from injury or destroy microrganism. By neutralizing the foreign agent and removing cellular debris and dead cells, repair of the injured area is able to proceed at a faster pace. Whether the damage is due to pathogens, chemicals, or physical trauma, the damaged tissue releases a number of chemical mediators that act as an alarms to notify the surrounding area of the injury.

Chemical mediators of inflammation include histamine, leukotrienes, bradykinin, complement, and prostaglandins. Some of these inflammatory mediators are important targets for anti-inflammatory drugs. Signs of inflammation include swelling, pain, warmth, and redness of the affected area. Inflammation may be classified as acute or chronic. Acute inflammation has an immediate onset and 8 to 10 days are normally needed for the symptoms to resolve and for repair to begin. If the body cannot contain or neutralize the damaging agent, inflammation may continue for long periods and become chronic.

Self assessment 1.7

1. What happens to the human body when an inflammation doen't resolve?
2. What are Chemical mediators of the inflammation?

1.8 Anti-Inflammatory Drugs

Learning Activity 1.8

Use library textbooks and respond to the following questions:

1. Enumerate commonly used anti-inflammatory drugs
2. Explain the mechanism of action of Nonsteroidal anti-inflammatory drugs
3. List the side effects of anti-inflammatory drugs

CONTENT SUMMARY

Anti-inflammatory agents are drugs that block the effects of the inflammation. The inflammatory response is the body's nonspecific response to cell injury, resulting in pain, swelling, heat, and redness in the affected area. Anti inflammatory drugs have antipyretic effect by blocking fever, often by direct effects on the thermoregulatory center in the hypothalamus or by blockade of prostaglandin

mediators. Antinflammatory drugs include **nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, acetic acid classes**

Nonsteroidal anti-inflammatory drugs are that widely used**.** They act by blocking prostaglandin synthesis and acting as anti-inflammatory, antipyretic, and analgesic agents. The NSAIDs are rapidly absorbed from the GI tract, reaching peak levels in 1 to 3 hours. They are metabolized in the liver and excreted in the urine. NSAIDs cross the placenta and cross into breast milk. Therefore, they are not recommended during pregnancy and lactation because of the potential adverse effects on the fetus or neonate.the general side effects of NSAIDs include: Bleeding, Gastric abset and reduced kidney function . There are two main classes of antinflammatory drugs including propionic acids and acetic acids**.**Among the propionic acid drug; **ibuprofen** is the mostly used drug to treat inflammation.

Inhibits prostaglandin synthesis by blocking Cyclooxygenase-1 and -2 receptor sites, leading to an anti-inflammatory effect, analgesia, and antipyretic effects for this it decreases swelling, pain, inflammation and fever. It is indicated to relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis; relief of mild to moderate pain; treatment of primary dysmenorrhea and fever.

Ibuprofen is available as tablets (A, B, C) either 200mg or 400mg per tablet and oral solution (D, E) In adults, ibuprofen dose is 400 mg tid or qid with the maximum of 1,200 mg/day and for pediatric clients the dosage is 5 - 10mg/kg 6-8hrly the maximum being 30mg/kg/day. Ibuprofen has a half-life of 1.8 to 2.5 hours. It is metabolized in the liver and excreted in the urine.The commonly **adverse effect of ibuprofen** includes headache, dizziness, somnolence, fatigue, rash, nausea, dyspepsia, bleeding, drug-induced peptic ulcer, constipation. Ibuprofen is a pregnancy category C before the first 30weeks of gestation and D from 30 weeks.

Figure 1.8.1 Iburpfen forms

Diclofenac and indomethacin are acetic acid derivative Nonsteroidal anti-inflammatory drugs. Diclofenac is a phenylacetic acid derivative while indomethacin is an indoleacetic acid derivative. Diclofenac is Analgesic, anti-inflammatory that acts by blocking the activity of cyclooxygenase, the enzyme needed to synthesize prostaglandins, which mediate inflammatory response and cause local pain, swelling, and vasodilation. By blocking cyclooxygenase and inhibiting prostaglandins, Diclofenac reduces inflammatory symptoms. This mechanism also relieves pain because prostaglandins promote pain transmission from periphery to spinal cord.

Diclofenac is indicated for the treatment of acute and chronic pain associated with inflammatory conditions in adults. In adults, diclofenac is prescribed as 50 mg t.i.d., p.r.n or bid–qid with the maximum of 200 mg per day, 100 mg for first dose only. The half-life is 2hours. The dose is reduced, if needed, for elderly patients and those with serious renal dysfunction. For injectable, the dosage is 2mg/kg/day resulting approximately in 1ampoule bid the half-life being 1.15 hours for suppositories 100mg bid is prescribed and the half is 3 to 6 hours. Patches for topical application, one patch is applied bid to the most painful area 12 hours.

Diclofenac is contraindicated for persons with active GI bleeding or ulcers; asthma attacks, rhinitis, or urticarial from aspirin or other NSAIDs, hypersensitivity to diclofenac or NSAIDs; treatment of perioperative pain after coronary artery bypass grafting. It is a Pregnancy category B drug. Indomethacin Relief of moderate to severe pain in PO 25 to 50 mg b.i.d. to q.i.d., increased by 25 or 50 mg daily every week, if needed the maximum being 200 mg daily. Diclofenac comes as an oral capsule (A, B), oral tablet (C), injectable (D, E) topical gel(G), suppository(H), transdermal patch (I), topical solution, and powder packets for oral solution (Figure 1.8.2)

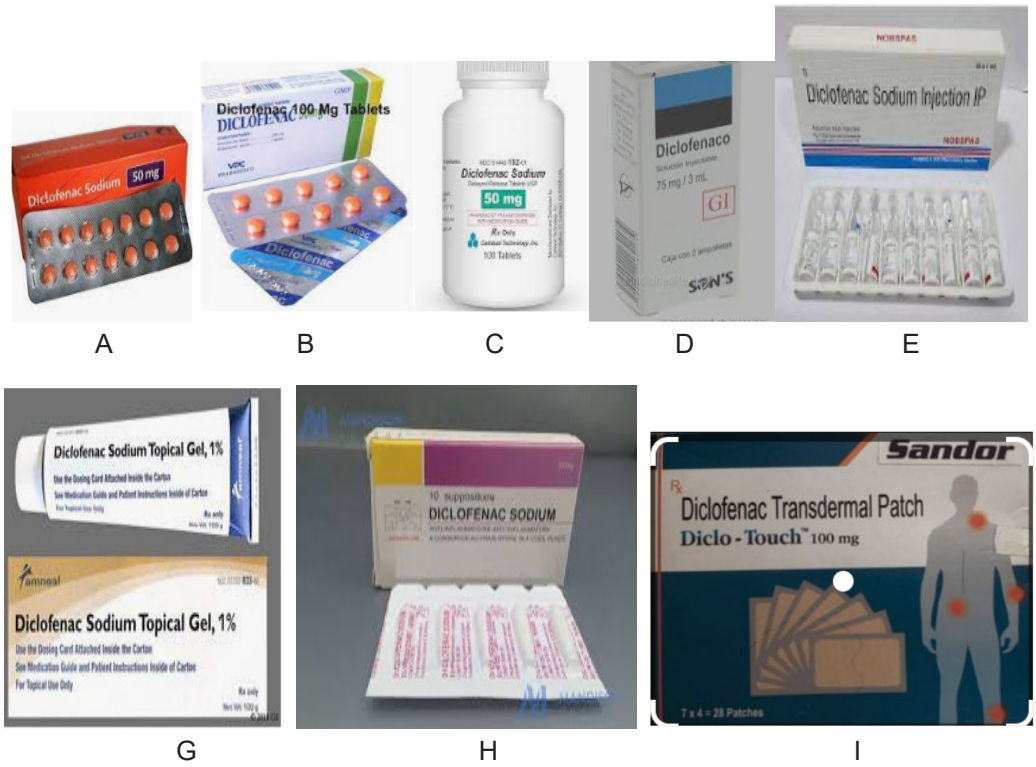


Figure 1.8.2: Diclofenac forms

Salicylates are salicylic acid compounds used as anti-infl ammatory, antipyretic, and analgesic agents.They inhibit the synthesis of prostaglandin, which is an important prostaglandin mediator of pyrogens at the thermoregulatory center of the hypothalamus.They are most popular and oldest anti-inflamamtory drugs with antipyretic and analgesic properties. They are generally available without prescription and are relatively nontoxic when used as directed. Salicylates are readily absorbed directly from the stomach, reaching peak levels within 5 to 30 minutes. They are metabolized in the liver and excreted in the urine. The half-life of 15 minutes to 12 hours, depending on the salicylate.

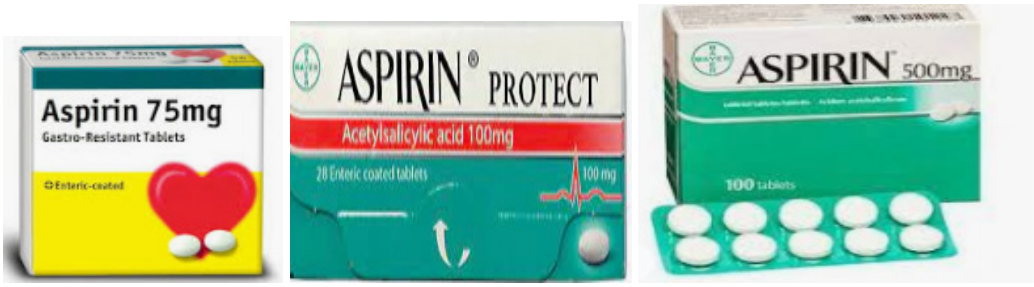
Salicylates cross the placenta and enter breast milk; they are not indicated for use during pregnancy or lactation because of the potential adverse effects on the neonate and associated bleeding risks for the mother. Salicylates should not be used by people with known allergy to salicylates or other nonsteroidal anti-inflammatory drugs and those with active bleeding. It is the same for patients presenting nasal polyps, history of asthma, chiken pox or influenza,surgery or othe invasive procedures within 1 week as this may lead to bleeding . They are not used by pregnant and lactating mothers and persons with renal impairement.

The adverse effects associated with salicylates results from its direct effects on the stomach and these include nausea, dyspepsia, heartburn, epigastric discomfort or its effect on clotting. When administered at higher levels, a salicysm syndrome arises with dizziness, ringing in ears, difficult in breathing, nausea, vomiting, diarrhea and mental confusion. Salicylate toxicity also occur when a dose of 20to 25g in adults or 4g in children is administered and the signs include hyperpnea, tachypnea, hemorrage, excitement, confusion, pulmonary edema, convulsion, tetany, acidosis, fever, cardiovascular, renal and respiratory collapse.

Aspirin is the most commonly used salicylate. At lower level, it affects platelet aggregation by inhibiting the synthesis of thromboxane A2, a potent vasoconstrictor that normally increases platelet aggregation and blood clot formation. At higher levels, aspirin inhibits the synthesis of prostacyclin, a vasodilator that inhibits platelet aggregation. Salicylates are indicated for the treatment of mild to moderate pain, fever, and numerous inflammatory conditions, including rheumatoid arthritis and osteoarthritis.

Aspirin inhibits the synthesis of prostaglandins by blocking the effects of pyrogens at the hypothalamus and inhibiting platelet aggregation by blocking thromboxane A2. The management of mild to moderate pain, fever, inflammatory conditions; reduction of risk of transient ischemic attack or stroke and reduction of risk of myocardial infarction. The half-life of aspirin is 15 minutes to 12 hours.It is metabolized in the liver and excreted in the urine. Aspirin is available in oral tablet of 75mg,100mg and 500mg.

In adults the dose is 350–650 mg every 4 h with the maximum of 4 gr per day. For children ages 2 to 14, 10 to 15 mg/kg/dose every 4 hr, p.r.n., up to 80 mg/kg daily. Pregnancy category: D. The adverse effects of aspirin include nausea, vomiting, heartburn, epigastric discomfort, occult blood loss, dizziness, tinnitus, acidosis.



A B C

Figure 1.8.3: Aspirin forms

Self assessment 1.8

Read carefully the text

You are working as nurse at RUBONA health center and you receive 2 clients in consultation room. The client's name is Mr. H aged 34 years old a man, who complains the swelling on the left leg after has been hit by a wood 3days ago, while he was cutting a tree in his farm. He has joint pain for 1 week has no fracture but the site is very hot and pain full with swelling. He has no history of other diseases.

The second client is Miss N. aged 19 years old, who complains pelvic pain with prostration but has normal vital signs. While you are taking history, she tells you that she is on her first day of menstruation and she started feeling the pain soon before menses start. Data obtained from the assessment and physical examination revealed no any other problems noticed except the tenderness in hypogastric region.

You are requested to manage these 2 patients' problems.

1. Which problem does Mr. H has? Discuss how the problems of Mr. H should be managed?
2. A. Discuss how the problems of Miss N can be treated?

   B. Is there any drug to avoid if yes why?

1.9 Medications for common cold and rhinitis

Learning Activity 1.9

Using library textbooks and internet, take note and respond to the following questions.

1. What are the group of medication for common cold management? Give an example of each group.
2. Describe the mechanism of action of anti-histamines drugs.

CONTENT SUMMARY

The treatment of **common cold** consists of **antihistamines, anti-inflammatories and decongestant drugs**. The signs and symptoms of allergic rhinitis resemble those of the common cold. They include tearing eyes, sneezing, nasal congestion, postnasal drip, and itching of the throat. The Goal of treating rhinitis aims at preventing its occurance and relieve the present symptoms.The drugs used to treat rhinitis are categorized into two groups.

The Preventers which drugs used as prophylaxis include **antihistamines, intranasal corticosteroids, and mast cell stabilizers.**

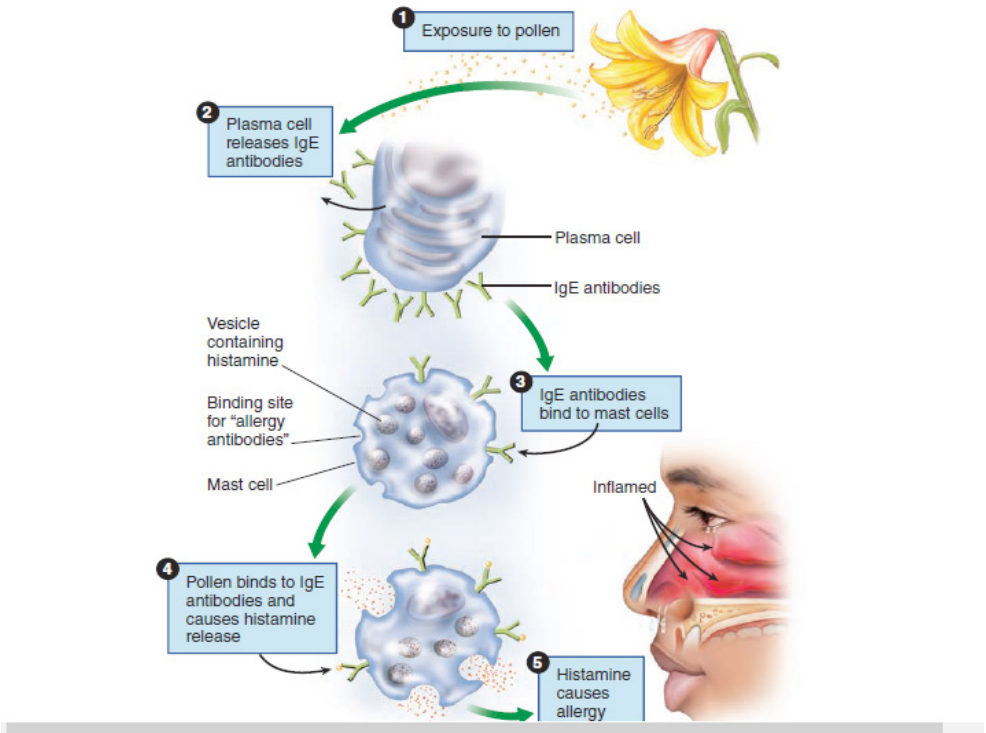


Figure 1.9.1. Histamine action and body's reactions

The Relievers are used to provide immediate, though temporary, relief for acute allergy symptoms once they have occurred. Relievers include the **oral and intranasal decongestants,** usually drugs from the sympathomimetic class. In addition to treating allergic rhinitis with drugs, nurses should help patients identify sources of the allergies and recommend appropriate interventions. These may include removing pets from the home environment, cleaning moldy surfaces, using microfilters on air conditioning units, and cleaning dust mites out of bedding, carpet, or couches.

The histamine receptors responsible for allergic symptoms are called H1 receptors. The other major histamine receptor, H2, is found in the gastric mucosa and is responsible for peptic ulcers .Antihistamines are drugs that selectively block histamine from reaching its H1 receptors, there by alleviating allergic symptoms. Because the term *antihistamine* is nonspecific and does not indicate which of the two histamine receptors are affected, H1-receptor antagonist is a more accurate name.

In clinical practice, as well as in this text, the two terms are used interchangeably. The most frequent therapeutic use of antihistamines is for the treatment of allergies. These medications provide symptomatic relief from the characteristic

sneezing, runny nose, and itching of the eyes, nose, and throat of allergic rhinitis. Antihistamines are often combined with decongestants and antitussives in OTC cold and sinus medicines. The viruses that cause common cold cause inflammation of the upper respiratory tract, by initiating the release of histamine and prostaglandins.

The inflamation leads to the increase engorgement of mucous membranes by blood leading to tissue swelling and an increase in mucous production consequently, sinus pain, nasal congestion, runny nose,sneezing,watery eyes,scratching the throat and headache. In some people the eustachian tube's outlet is blocked and the ear becomme stuffed and painfull and more likely this results in otitis media. Rhinitis is an inflammation of nasal cavity. This condition occurs when the upper airways respond to a specific antigen like dust,pollen. The inflammatory response cause sneezing, nasal congestion, stuffness and waterly eyes. While the treatment of the treatment of rhinitis is antihistamines.

Antihistamines are drugs that block the release or action of histamine, a chemical released during inflammation that increases secretions and narrows airways in antihistamines drugs. Antihistamines are found in multiple out of the counter preparations that are designed to relieve respiratory symptoms and to treat allergies. When choosing an antihistamine, the individual patient's reaction to the drug is usually the governing factor.

Because first-generation antihistamines have greater anticholinergic effects with resultant drowsiness, a person who needs to be alert should be given one of the second-generation, less-sedating antihistamines. Because of their out of the counter availability, these drugs are often misused to treat colds and influenza. Those drug include the following: brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyclizine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, promethazine, triprolidine these are in the first Generation. Azelastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine are in the second generation. **Chlorpheniramine is a commonly used drug** in adults to treat simple common cold and rhinitis while in moderate and chronic cases,desloratidin is prefered.

Figure 1.9.2. Anti histamine Drugs

Decongestants are drugs that decrease the blood flow to the upper respiratory tract and decrease the overproduction of secretions.**Decongestants** decrease the overproduction of secretions by causing local vasoconstriction to the upper respiratory tract .This vasoconstriction leads to a shrinking of swollen mucous membranes and tends to open clogged nasal passages, providing relief from the discomfort of a blocked nose and promoting drainage of secretions and improved airflow.

An adverse effect that accompanies frequent or prolonged use of these drugs is a **rebound congestion**, technically called **Rhinitis medicamentosa**. The reflex reaction to vasoconstriction is a rebound vasodilation, which often leads to prolonged overuse of decongestants.They exist topical nasal decongestant with ephedrine as prototype, oxymetazoline, phenylephrine, oral decongestants pseudoepinephrine, topical nasol steroid decongestants such us beclomethasone, budesonide, dexamethasone, flunisolide is prototype.

Figure 1.9.3. Anti Decongestant Drugs

Table 1.9.1: Decongestant drugs and their indications

	Ephedrine(Pretz-D) spray
Indication and mode of use	Instal solutions in each nostril q4h,do not use for children <unless advised.
Adverse effects	Burning, soreness, dryness, stinging, itching or sneezing

	Oxymethazoline(Afrin,Allerest) spray
Indication and mode of use	Adult and pediatric (>6y), 2 to 3 sprays or drops in each nostril b.id Pediatric (2-5y): Two or three drops of 0.05 solutions in each nostril b.i.d

Adverse effects	Stinging, increased nasal discharge, dryness inside the nose, sneezing, nervousness, nausea,dizziness

	Phenylephrine(coricidin)spray
Indication and mode of use	Adult and pediatric (6y) one or two sprays each nostril q3-4h Pediatric (2-6y): Two to three drops of 0.125solution in each nostrile q4h as needed
Adverse effects	Temporary sneezing, mild burning, dryness, cold feeling or irritation inside the nose, headache, dizziness, weakness, feeling excited or resless or mild sleep problems

	Tetrahydrozoline(Tyzine) Spray
Indication and mode of use	Adult and pediatric(>6years): Two to four drops in each nostril t.i.d to q.i.d Pediatric (2-6 years): two to three drops of 0.05 solutioni each nostril q4-6h
Adverse effects	Temporary burning , stinging, dryness in the nose, runny nose and sneezing, feeling excited or resless or mild sleep problems

Oral Decongestant:

	Naphazoline(privine)
Indication and mode of use	2 drops every 3-6h
Adverse effects	Burning, stinging,sneezing, dryness, local irritation, rebound congestion

	Pseudo-ephedrine(Sudafed,Decofed)
Indication and mode of use	Adult 60 mg q4-6h Pediatric:6-12y:30mgPO q4-6h 2-5y:15mg PO q4-6h 1-2y:0.020ml/kgPOq4-6h 3-12 mo; three drops/kg PO q4-6h

Adverse effects	Feeling sick, heache, dry mouth, fast or irregular heartbeat or increased blood pressure

Topical steroid Nasal Decongestants:

	Beclomethazone (Beclovent)
Indication and mode of use	Adult: one to two inhalations in each nostril b.id Peditrict (6-11y): one inhalationin each nostril b.i.d
Adverse effects	Stinging or burning sensation in the nose, dryness, itchness, redness and swelling in the nose.

	Budesonide (Pulmicort)
Indication and mode of use	Adult and pediatric(> y6): two sparys in each nostril morning and evening or four sprays in each nostril the morning
Adverse effects	Stinging or burning sensation in the nose, dryness, itchness, redness and swelling in the nose.

Tables 1.9.2: summary of Anti histamine Drugs:

H1-Receptor antagonists First generation:

	Chlorpheniramine
Indication and mode of use	allergic conditions such as itchy and watery eyes, sneezing, runny nose, the fever and common cold Po, 2-4mg tid-qid(max: 24mg/day)
Adverse effects	Dry mouth, headache, dizziness, urinary retention, thickening of bronchial secretions, nausea and vomiting, sleeping

	Promethazine (phenergan)
Indication , route and dose	Anaphylactic reactions, sedation, nausea, vomiting, pain, motion sickness, and allergic skin reactions Po,12.5-25MG/DAY(max: 100mg/day)
Adverse effects	Paradoxical excitation, sedation, hypersentivity reactions, hypotension, extrapyramidal symptoms, respiratory depression

H1-Receptor antagonists second generation:

	Desloratidine (clarinex)
Indication , route and dose	Anaphylactic reactions, sedation, nausea, vomiting, pain, motion sickness, and allergic skin reactions Po, 5mg/day (max: 5mg/day)
Adverse effects	Dry mouth, headache, dizziness,drowniness,bitter taste

	Cetirizine (Zyrtec)
Indication , route and dose	Anaphylactic reactions, sedation, nausea, vomiting, pain, motion sickness, and allergic skin reactions. Po, 5-10mg/day (max: 10mg/day)
Adverse effects	Nausea

	Loratidine(claritin)
Indication , route and dose	Anaphylactic reactions, sedation, nausea, vomiting, pain, motion sickness, and allergic skin reactions. Po, 10mg/day
Adverse effects	Paradoxical excitation,hypersensitivity reactions, hypotension.

Intranasal corticosteroids:

	Beclomethasone (Beconase AQ, QnaslQvar)
Indication , route and dose	Anaphylactic reactions, sedation, nausea, vomiting, pain, motion sickness, and allergic skin reactions. Intranasal, 1-2 sprays in each one to four times daily
Adverse effects	Transient nasal irritation, burning, sneezing , dryness

Self assessment 1.9

Choose the best answer

1. Which drug among the following drugs is used in the treatment of common cold?
   A. Acetaminophen
   B. Tramadol
   C. Chlorphenamine
   D. Cimetidine
2. Among the drugs below, which one is an intranasal decongestant?
   A. Promethazine
   B. Beclomethasone
   C. Desloratidine
   D. Omeprazole
3. What is the **MOST COMMON** side effect of nasal decongestant?
   A. Nose bleeding
   B. Runny nose
   C. GI upset
   D. Burning sensations

1.10. Overview on pathophysiology of seizures

Learning Activity 1.10

1. Based on your observations what should be the problem expressed in pictures?
2. Using library textbooks, describe the physiology of seizures?

CONTENT SUMMARY

Seizures are uncontrolled electrical activity in the brain that may lead to symptoms ranging from mild loss of attention to violent muscular contractions that can lead to death. Everyone has the potential to have seizures or convulsion. The seizures occur when there is an abnormal electrical activity in the brain. They are also known as convulsions, but not all seizures produce convulsive behavior which is uncontrollable muscle contractions names as atonic seizures, Where there is a loss of muscular tone or strength.

The seizures' symptoms produced dependent on which part of the brain is experiencing the abnormal electrical activity. Seizures are generally short lived from 15 seconds to 15 minutes however; there is a life-threatening type of seizure, status epilepticus, in which the seizure does not end. A diversity of conditions and substances can Cause seizures. Common trigger causes seizures include congenital abnormalities of the brain, ellicit drug use, fever, brain tumors and metabolic imbalances, such as high levels of glucose or sodium. The epilepsy is known as a condition in which a person experiences repeated seizures, due to an overall electrical disturbance in the brain.

The terms **convulsion and seizure** are often used interchangeably and basically have the same meaning, each different type of seizure disorder is characterized by a specific pattern of events as well as a different pattern of motor or sensory manifestations Partial or focal seizures arise from a localized area in the brain and cause specific symptoms.

A partial seizure can spread to the entire brain and cause a generalized seizure. Partial seizures include simple seizures in which consciousness is not impaired.

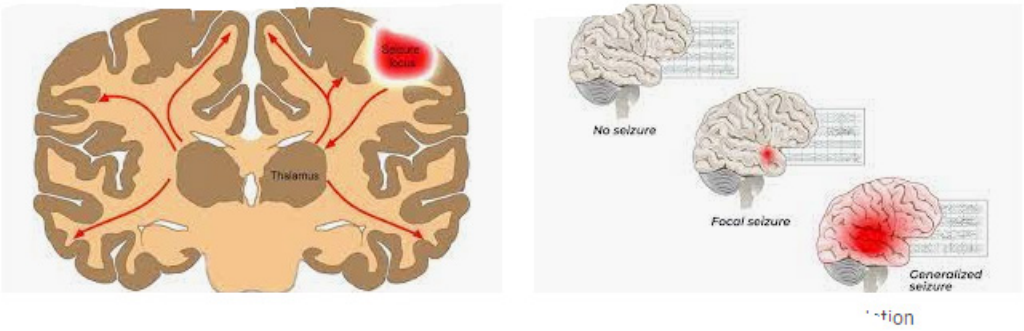


Figure 1.10.1 seizures transmission

Psychomotor seizures occur most often in children 3 years of age through adolescence. The individual may experience an aura with perceptual alterations, such as hallucinations or a strong sense of fear. Repeated coordinated but inappropriate movements, such as clutching, kicking, picking at clothes, walking in circles, and licking are characteristic. Generalized seizures include absence,

myoclonic, and tonic–clonics. Manifestations of a generalized **tonic–clonic** seizure include alternate contraction (tonic phase) and relaxation of muscles, a loss of consciousness, and abnormal behavior.

Myoclonic seizures involve sudden, forceful contractions involving the musculature of the trunk, neck, and extremities. **Absence seizures**, previously referred to as petit mal seizures, are seizures characterized by a brief loss of consciousness during which physical activity ceases. The seizures typically last a few seconds, occur many times per day, and may go unnoticed by others.

Classification of seizures

Focal Onset	General Onset	Tonic-clonic
Aware /impaired awareness	Motor Onset/non motor onset	Other motor
Focal to bilateral tonic	Unknown Onset	NonMotor(absentce)
		Unclassified

If patients have a lower tolerance to environmental triggers; seizures may occur when they are sleep deprived, are exposed to strobe or flickering lights, or have a fluid and electrolyte imbalance. Seizure disorders occur throughout the life span. Those who experience seizures, about half will experience their first seizure before age 10. Seizure in pregnant woman requires special education to either prevent conception or to safely prevent seizures during pregnancy. Seizure disorders in the older adult are most often associated with an underlying comorbid condition. Cerebrovascular disease, especially stroke, accounts for one third of all cases and is the most common risk factor for the development of epilepsy after age 6.

Febrile seizures are defined as seizures associated with fever in the absence of central nervous system infection. Febrile seizures are common among children and unusual in adults. In adults with hyperthermia above 40.5^{o}c, nerve damage coagulation of cell proteins leads to convulsions. The developing brain of child is very sensitive to effects of mild to high fever that led to abnormal discharge of electrical activity within the brain. The sudden rise in temperature seems to be more important than the degree of temperature. The seizure may occur with the initial onset of fever before a child's caregiver is even aware the child is ill. Most febrile seizures are generalized when they involve the whole body.

In other words, the whole body may be involved and Stiffening of the entire body Jerking of the arms and legs, complete lack of response to any stimuli, eyes deviated, staring, rolling back, moving back and forth, tightness of the jaws and mouth, urinary incontinence, noisy breathing, labored, slower than normal (unusual for a child to stop breathing completely).

Although it may seem like infinity if you are observing a seizure, most of these episodes last only 1-5 minutes. Afterward, the child is typically drowsy but usually starts to become responsive within 15-30 minutes. Seizures may be focal when one part of the body is involved.

Self assessment 1.10

1. Which of the following mostly triggers the seizures
   A. Fever
   B. Running
   C. Pregnancy
   D. Old age
2. What are the manifestations of Tonic- clonic seizures? Choose the correct answer
   A. Acute kidney injury
   B. Abnormal bleeding
   C. Loss of consciousness
   D. Severe pain
3. True or False
   A. The seizures occur when there is an abnormal electrical activity in the brain
   B. Partial seizures can lead to generalized seizures
   C. The young children are at higher risk of seizures associated with fever because their developing brain is less sensitive to effects of mild to high fever.

1.11. Medications for seizures

Learning Activity 1.11

Use library textbooks, take note and respond to the following questions

1. What are the class of antiseizures? Give an example of medication on each class.
2. What are the common side effects of antiseizures drugs?

CONTENT SUMMARY

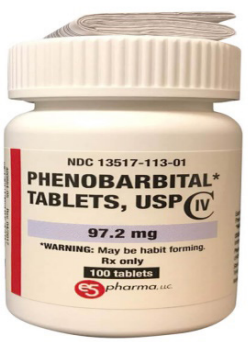
Medications for the management of seizure disorders are called antiseizures. Most anti-seizures have specific uses; that is, they are of value only in the treatment of certain types of seizure disorders. There are four categories of drugs used

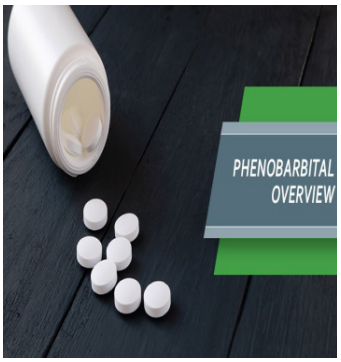
as anticonvulsants: **barbiturates, benzodiazepines, hydantoins, and the succinimides**, generally, anticonvulsants reduce the excitability of the neurons (nerve cells) of the brain. When neuron excitability is decreased, seizures are theoretically reduced in intensity and frequency of occurrence or, in some instances, are virtually eliminated.

Barbiturates medications are the chemical derivatives of barbituric acid. These drugs reduce neuronal excitability primarily by increasing GABA-mediated inhibition through GABA RECEPTORS. They act on spinal cord, brainstem and the Heightened GABAergic transmission at motor neurons in the spinal cord relaxes muscles and suppresses reflexes:

Table 1.11.1: Phenobarbital

	Phenobarbital
Route and dose	P.O 50-100mg b.i.d-tid
Adverse effects	Drowsiness, headache, dizziness, excitement or increased activity, nausea, vomiting





Benzodiazepine antiseizures drugs act by potentiating GABA binding by increasing the frequency of channel opening in the presence of low GABA concentrations, and, at GABA concentrations similar to those in synapses receptor deactivation is slowed. Benzodiazepines drugs are not only used control seizures but also for the

treatment of anxiety, skeletal muscle spasms, and alcohol withdrawal symptoms. Most benzodiazepines are given orally Those that can be given parenterally, such as diazepam (Valium) and lorazepam (Ativan), should be monitored carefully owing to their rapid onset of CNS effects, and possible respiratory depression.

Benzodiazepines are contraindicated in patients with known hypersensitivity to the drugs. Benzodiazepines are also contraindicated in patients with acute narrow-angle glaucoma, psychosis, liver or kidney disease, and neurological disorders. Benzodiazepines should be used cautiously during pregnancy

Adverse effects of benzodiazepines are drowsiness, ataxia, impaired judgment, dry mouth, fatigue, visual disturbances, rebound insomnia, and development of tolerance. Overdosage may result in CNS and respiratory depression as well as hypotension and coma. Gradual withdrawal of these drugs is recommended. Although the use of any of the benzodiazepines during pregnancy is likely to cause fetal abnormalities, flurazepam is entirely contraindicated during pregnancy. As it is category D, and in elderly or debilitated patients.

Benzodiazepines increase CNS depression with alcohol and omeprazole. They also increase pharmacological effects if combined with cimetidine, disulfiram, or hormonal contraceptives. The effects of benzodiazepines decrease with theophylline and ranitidine.

Tables1.11.2. Benzodiazepine antiseizures

	Diazepam (Valium)
Route and dose	PO, 2 - 1 0 mg bid; IM/IV, 2-10 mg: repeat if needed in 3 - 4 h
Adverse effects	Drowsiness, dizziness, tiredness, muscle weakness, headache, dry mouth, nausea, constipation

	Lorazepam ((Ativan)
Route and dose	PO; 2 - 6 mg/day in divided doses (max: 10 mg/day)
Adverse effects	Drowsiness, dizziness, tiredness, weakness, dry mouth, diarrhea, nausea and change in appetite

	Clonazepam (Klonopin)
Route and dose	PO; 1 - 2 mg/day in divided doses (max: 4 mq/day)
Adverse effects	Drowsiness, dizziness, unsteadiness, problems with coordination, difficult thinking or remembering, increased saliva, muscle and joint pain, frequent urination

Figure 1.11.1: Benzodiazepine antiseizures

Hydantoins are a class of drugs mainly used to treat seizures (anticonvulsant or antiepileptic drugs). They reduce seizures by targeting the sodium channel present throughout the nerves. They act by desensitizing sodium channels in the CNS responsible for neuronal responsiveness. This desensitization prevents the spread of disruptive electrical charges in the brain that cause seizures.

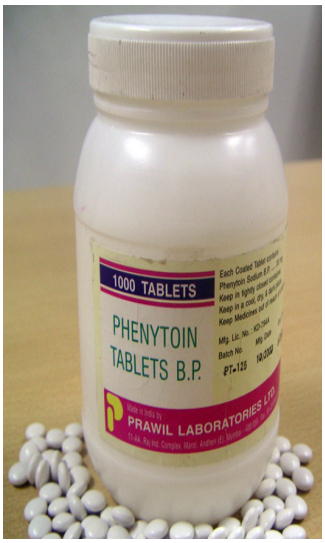
Phenytoin is used for tonic-clonic seizures, psychomotor seizures, and seizures after head trauma. Fosphenytoin is converted to phenytoin in the body and is parenterally used for control of status epilepticus; it is a short term substitute for oral phenytoin.

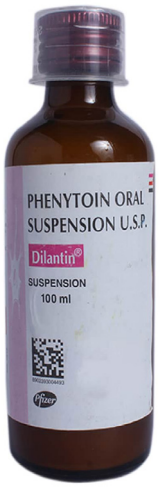
Tables 1.11.3. Hydantoins Antiseizures:

	Phenytoin(dilantin)
Route and dose	PO; 15-18 mg/kg of 1-g initial dose; then 300 mg/day in 1 - 3 divided doses; may be gradually increased 100 mg/week The intravenous injection also is available.
Adverse effects	Agranulocytosis, aplastic anemias ; purpuric dermatitis; Stevens-Johnson syndrome; toxic epidermal necrolysis; cardiovascular collapse; cardiac arrest

	Carbamazepine (Tegretol)
Route and dose	P0; 200 mg bid, gradually increased to 800-1,200 mg/day in 3 - 4 divided doses
Adverse effects	Dizziness, ataxia, somnolence, headache, diplopia, blurred vision, transient indigestion, rhinitis, leukopenia, prolonged bleeding time, nausea, vomiting, anorexia

	Valproic acid (Depakene)
Route and dose	PO/IV; 15 mg/kg/day in divided doses when total daily dose is greater than 250 mg; increase 5-10 mg every week until seizures are controlled (max: 60 mg/kg/day)
Adverse effects	Stomach pain, diarrhea, dry or sore mouth, swollen gums, tremors in a part of the body, unusual eye movements, feeling tired or sleepy, headache, weight gain, thinning hair, or change in colour or texture of your hair





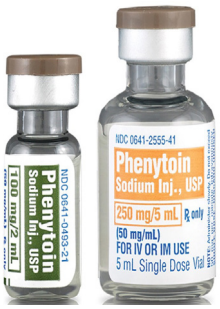


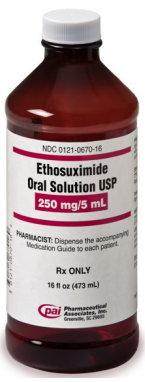
Figure 1.11.2: Form of hydantoins antiseizures

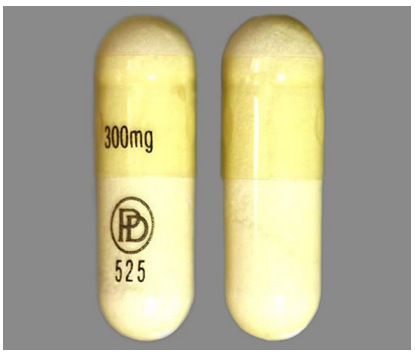
Succinimides antiseizures act by delaying the entry of calcium into neurons by blocking calcium channels and inhibit neuronal systems. They increase the electrical threshold. Succinimide drugs are used to control absence seizures and myoclonic seizures. They may be given in combination with other anticonvulsants.

Table 4. Succinimide antiseizures drugs:

	Ethosuximide (Zarontin®)
Route and dose	P.O, 250 mg b.i.d., increased q4–7 days (max: 1.5 g/day)
Adverse effects	Cramps, drowsiness, hiccpus , nausea, vomiting, discomfort in the chest upper stomach or throat, weakness

	Methsuximide (Celontin®)
Route and dose	P.O, 300 mg/day, may increase q4–7 days (max: 1.2 g/day in div. doses)
Adverse effects	Nausea, vomiting, constipation or diarrhea ,stomach pain, loss of appetite, weight loss, hiccups





***Forms of* Succinimide antiseizures**

The common side effects of antiseizures drugs are: poor concentration, short term memory loss, drowsiness, fatigue, hyperactivity, Visual problems (blurred or double vision), speech problems, poor coordination and balance, dizziness and unsteadiness, nausea, vomiting and weight gain or loss.

Self assessment 1.11

1. Which of the following is a barbiturate anti -seizure?
   A. Diazepam
   B. Carbamazepine
   C. Phenobarbital
   D. Valproic acid
2. Among class of antiseizures drugs act by potentiating GABA binding capacity
   A. Barbiturates
   B. Benzodiazepine
   C. Succinimides
   D. Hydantoins
3. Among class of antiseizures drugs act by delaying the entry of calcium into neurons.
   A. Barbiturates
   B. Benzodiazepine
   C. Succinimides
   D. Hydantoins
4. One of the following hydantoins antiseizures has a side effect of prolonging the bleeding time. Select the best answer
   A. Tegretol
   B. Dilantin
   C. Depakene
   D. Valproic acid

End of unit assessment1

1. Which of the following statements indicates the properties of paracetamol?
   A. Paracetamol has strong anti-inflammatory effect compared to ibuprofen or aspirin
   B. Paracetamol is a commonly used antipyretic and may have an analgesic effect
   C. Paracetamol belongs to a wide class of non-steroidal anti-inflammatory medications
   D. Paracetamol may be classified in pregnancy category C drugs like aspirin.
2. Nociceptive pain or physiological pain may be described as an abnormal reaction to stimuli caused by damaged nerves. True or False.
3. Name three main classes of anti-inflammatory agents

   Answer: nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, acetic acid classes
4. Which of the following enzymes is blocked by ibuprofen to exert its anti-inflammatory action?
   A. Cyclo-oxygenase
   B. Monoamine oxidase
   C. Deoxyribonuclease
   D. Glucose isomerase
5. Which of the following anti-inflammatory drugs is classified among the salicylates?
   A. Diclofenac
   B. Ibuprofen
   C. Aspirin
   D. Indocid
6. Which of the following antiseizure medications may be classified among the barbiturates?
   A. Lorazepam
   B. Clonazepam
   C. Carbamazepine
   D. Phenobarbital
7. What are the three main classes of medications used in the management of common cold?
   A. Antihistamines, anti-inflammatories and anticonvulsant drugs .
   B. Antihistamines, anti-inflammatories and decongestant drugs .
   C. Antihistamines , anti-inflammatories and antiretroviral drugs .
   D. Antihistamines , anti-inflammatories and antibiotic drugs .

8. What are the features of salicysm syndrome that results from the use of higher doses of salicylates?
   A. Dizziness, ringing in ears, difficult in breathing, nausea, vomiting, diarrhea and mental confusion
   B. Dizziness, ringing in ears, difficult in breathing, nausea, vomiting, high fever and alertness
   C. Alertnes, dizziness, ringing in ears, difficult in breathing, nausea, vomiting, and tachycardia
   D. Dizziness, ringing in ears, difficult in breathing, nausea, vomiting, skin lesions and alertness
9. All of the following are the examples of local anaesthetics, EXCEPT:
   A. Benzocaine,
   B. Cloroprocaine
   C. Tetracaine
   D. Penicillin procaine
10. Antipyretic Causes decreased platelet aggregation and causes gastric ulcers is
   A. Diclofenac
   B. Ibuprofen
   C. Aspirin
   D. Paracetamol
11. Which of these is not a purpose of inflammation?
   A. Destroy the cause of inflammation
   B. Isolate the cause of inflammation
   C. Initiate tissue repair
   D. Alert the organism of infection
12. Why most of medications for inflammation are treating at the same fever?
13. Case study: NG is a 26 years old man who presents to Remera health center for consultation where you are working today as a nurse. The patient is complaining of fever, headache, and chills for 2days. You took vital signs and found that axillary temperature is 40. 9^0c; pulse was 70beats/min, respiration 22 cycles per minutes, blood pressure 100/72 mmhg and has the pain of 6/10 on numeric scale, his weight is 65kg. Mr. NG declared that he has history of gastritis, soon after he started shaking, finally got convulsion.
   i. List all medications you will use to manage this case and give the reasons. Indicate the specific and drug, dosage
   ii. Which medications will you avoid to use? Why?

UNIT 2: ANTIBIOTICS

Key Unit competence:

Manage different health conditions at the primary healthcare settings by utilizing antibiotics appropriately.

Introductory activity 2.0

The images below show different patients with bacterial infections and they are being treated with different medications.

1) Have you even seen such kinds of patients?
2) If yes, what types of drugs you heard or saw they were taking?
3) Have you ever seen some types of the drugs in these images?

2.1. Definition of antibiotics and key concepts

Learning Activity 2.1

1) Read the scenario below:

A 37-year-old female patient takes drugs every eight hours. She was told that she has a disease that requires to be taken for 10 consecutive days. Not all details were provided by the healthcare providers, and she heard from different people that both antimicrobial and antibiotic agents may be used for an extended period of time that can go beyond 10 days. She then doubts whether she is taking an antibiotic or antimicribial, and wants to get your view. Answer the questions below:

a) In details, differentiate antibiotic from antimicrobial agents

b) Give a difference between broad spectrum and narrow spectrum antibiotics

CONTENT SUMMARY

Antibiotics are medicines that fight bacterial infections in people and animals. They work by killing the bacteria or by making it hard for the bacteria to grow and multiply.

Examples: Amoxicillin, Gentamicin, Cotrimoxazole.

An antimicrobial is a drug used to treat a microbial infection. “Antimicrobial” is a general term that refers to a group of drugs that includes antibiotics, antifungals, antiprotozoals, and antivirals. The antibiotics belong to the wide class of antimicrobials.

Examples: Ketoconazole (antifungal), Metronidazole (antiprotozoal), and acyclovir (Antiviral).

Antibiotic drugs can be bacteriostatic or bactericidal.

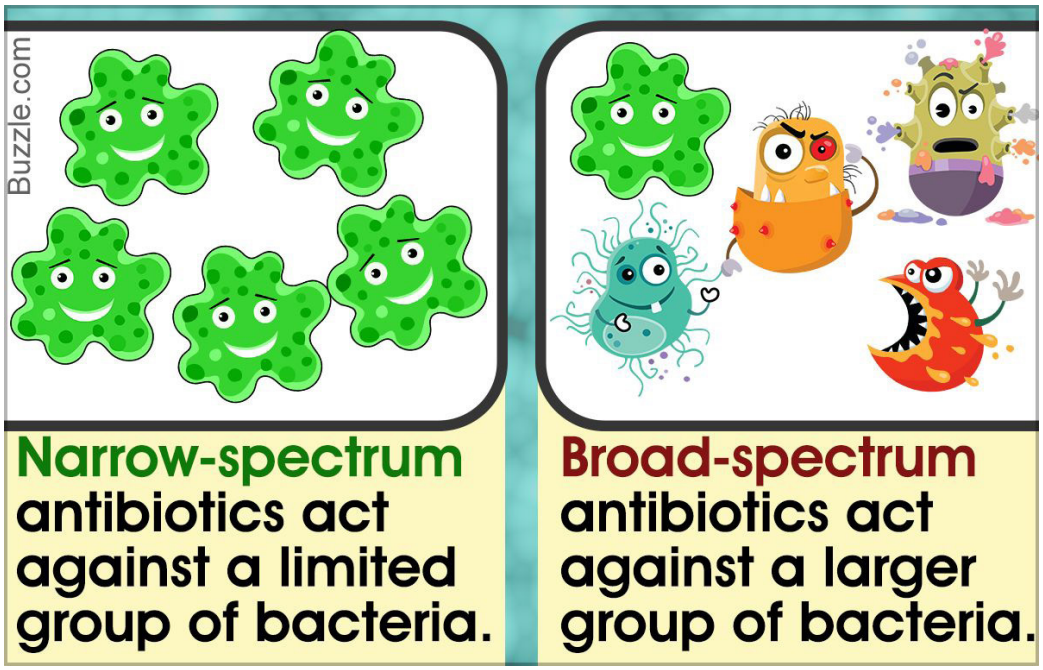
"Bacteriostatic" refers to the ability of the agent (antibiotic) to prevent the growth of bacteria while "bactericidal" is the ability of the agent to kill bacteria.

However, several antibiotics are both bactericidal and bacteriostatic, depending on the concentration of the particular drug.

There is no perfect antibiotic that is without effect on the human host. Therefore, health personnel try to select an antibiotic with selective toxicity, which is the ability to strike foreign cells with little or no effect on human cells.

Antibiotics may be classified as having broad spectrum of activity or narrow spectrum of activity. Narrow-spectrum antibiotics act against a limited group of bacteria while broad-spectrum antibiotics act against a larger group of bacteria.

Difference between narrow-spectrum and broad-spectrum antibiotics



Self-assessment 2.1

1) A colleague of class tells you that he is swallowing capsules of amoxicillin as an antibiotic after having sustained an injury that developed pus. The colleague wants to know what an antiotic is, and what it is used for. What will you tell your colleague?

2) Is there any relevance in prescribing such drug to your colleague?

2.2. Ideal antibiotics and Mechanism of action of antibiotics

Learning Activity 2.2

1) Read carefully the scenario below:

A 62-year-old female is admitted at the healthcare facility with features of an infection. The laboratory investigations help to identify the causal agent of the bacterial infection, and an appropriate antibiotic is prescribed basing on the identified agent. The reason to choose the drug was mainly based on the mechanism of action of the prescribed antibiotic against the infectious bacterial agent. In addition, the healthcare provider chose an antibiotic basing on its characteristics.

a) Describe the qualities of an ideal antibiotic the nurse will consider while prescribing the antibiotic.

b) List the 5 main mechanisms of action of antibiotics?

c) Is it required to consider the mechanism of action of an antibiotic during its prescription? Explain your answer.

Guidance: Read the book of pharmacology brought by the teacher in class, on topic of mechanism of action of antibiotics.

CONTENT SUMMARY

An ideal antibiotic is an antibacterial agent that kills or inhibits the growth of all harmful bacteria in a host, regardless of site of infection without affecting beneficial gut microbes (gut flora) or causing undue toxicity to the host. Ideal antibiotics should be toxic to microbes, and not to humans, bactericidal rather than bacteriostatic, effective against broad range of bacteria; active in placenta, and other body fluids; cost effective; and should not cause allergic and hypersensitive reactions, should not give drugs resistance, long shelf life; and desired levels should be reached rapidly and maintained for adequate period of time.

The antibiotics exert their effects through different mechanisms that alter or damage the bacterial cell. This disruption of the bacterial cell function ends up in the death of the bacteria, which is an expected outcome of the treatment with antibiotics. This is made possible by the fact that bacterial prokaryotic cells have some differences with the human cells, and the former become the target of antibiotic drug action.

Several different classes of antibacterials use a mechanism of “Inhibition of bacterial cell wall synthesis” by blocking steps in the biosynthesis of **peptidoglycan**, making cells more susceptible to osmotic lysis. Therefore, antibacterials that target cell

wall biosynthesis are bactericidal in their action. Because human cells do not make peptidoglycan, this mode of action is an excellent example of selective toxicity.

A small group of antibacterials alter the bacterial cell membranes in their mode of action. They interact with lipopolysaccharide in the outer membrane of gram-negative bacteria, killing the cell through the eventual disruption of the outer membrane and cytoplasmic membrane. For gram-positive bacteria, these antibacterials insert into the cytoplasmic membrane of the bacteria, disrupting the membrane and killing the cell.

Other antibacterials inhibit bacterial protein synthesis. The cytoplasmic **ribosomes** found in animal cells (80S) are structurally distinct from those found in bacterial cells (70S), making protein biosynthesis a good selective target for antibacterial drugs.

Some synthetic drugs control bacterial infections by functioning as **antimetabolites**, competitive inhibitors for bacterial metabolic enzymes. In their mechanism of action, these antibiotics may inhibit the enzyme involved in production of dihydrofolic acid, they may inhibit the enzyme involved in the production of tetrahydrofolic acid or interfere with the synthesis of mycolic acid.

Finally, some antibacterial drugs work by inhibiting bacterial nucleic acid synthesis. In this case, these antibiotics inhibit bacterial RNA polymerase activity and blocks transcription, killing the cell. Alternatively, they inhibit the activity of DNA gyrase and blocks DNA replication, killing the cell.

Self-assessment 2.2

Read the scenario below:

A 25-year-old female patient comes to the health post where you work. She comes 3 days after starting treatment with antibiotics, complaining of additional symptoms after starting the treatment. She reports severe diarrhea, nausea, vomiting, many skin rashes, and difficult swallowing. The nurse receiving the patient decided to change the antibiotic for the patient, and managed the additional complaints. The patient recovered after a short period of time.

1) In your understanding, was it necessary for the patient to come back to the health post?
2) Was the first drug ideal antibiotic to the patient?
3) All of the following are the mechanisms of action of antibiotics, Except:
   a) Inhibiting bacterial nucleic acid synthesis
   b) Alter the bacterial cell membranes
   c) Inhibit bacterial protein synthesis
   d) Acting as bacterial metabolites
4) As human cells make peptidoglycan, this prevents the antibiotics from exerting their selective toxicity effect. True or False

2.3. Drug resistance and prevention of antibiotic drug resistance

Learning Activity 2.3

1. Read carefully the scenario below:

A 17-year-old female adolescent was involved in unprotected sexual intercourse and got infected with sexually transmitted bacteria. She consulted the nearest health post and doxycycline has been prescribed as antibiotics to be taken BID for 14 days. After taking first dose, she complained that the drug tasted badly and refused to continue taking the drug. After 4 days, she felt severe pain in lower abdomen with painful urination. She then took other 3 doses, the symptoms reduced, and she stopped again. After the period of 1 month, she felt again similar severe pain and consulted another health post and she was given the same drug (doxycycline). She decided to take completely and correctly the prescribed drug but after the completion of prescribed doses, the symptoms persisted. She decided to consult the hospital to give sample for culture and sensitivity. The laboratory results showed that doxycycline could not cure the disease because microbes had developed the resistance against doxycycline.

a) According to you, what mistakes did the adolescent commit in taking the initially prescribed drug?

b) Referring to the scenario above, how can antimicrobial drug resistance develop? Explain your answer?

c) What type of resistance did this adolescent develop?

Guidance: Read the book on topic of antibiotic resistance provided by the teacher, and answer the questions above.

CONTENT SUMMARY

Antimicrobial resistance may develop anytime, when necessary, measures while using antimicrobials are not taken. In nature, microbes are constantly evolving in order to overcome the antimicrobial compounds produced by other microorganisms. Human development of antimicrobial drugs and their widespread clinical use has simply provided another selective pressure that promotes further evolution. Several important factors can accelerate the evolution of **drug resistance**. These include the overuse and misuse of antimicrobials, inappropriate use of antimicrobials, sub-therapeutic dosing, and patient noncompliance with the recommended course of treatment. Resistance can be natural or acquired.

Anti-infectives act on specific enzyme systems or biological processes. On one hand, many microorganisms that do not use that system or process are not affected

by a particular anti-infective drug. They are said to have a natural or intrinsic resistance. On the other hand, microorganisms that were once very sensitive to the effects of particular drugs have begun to develop acquired resistance to the agents. This is known as acquired resistance.

With the current use of antibiotics in humans and animals, emergence of resistant strains of microbes is becoming a serious public health problem. Health care providers must work together to prevent this issue, given that exposure to an antimicrobial agent can lead to the development of resistance. It is therefore important to limit the use of antimicrobial agents to the treatment of specific pathogens known to be sensitive to the drug being used. Drug dosing is important in preventing the development of resistance, and doses should be high enough and the duration of drug therapy should be long enough to eradicate even slightly resistant microorganisms.

Around-the-clock dosing eliminates the peaks and valleys in drug concentration and helps to maintain a constant therapeutic level to prevent the emergence of resistant microbes during times of low concentration. The duration of drug use is critical to ensure that the microbes are completely, not partially, eliminated and are not given the chance to grow and develop resistant strains.

It was identified that it is difficult to convince people who are taking anti-infective drugs that the timing of doses and the length of time they continue to take the drug are important. There is a need to be cautious about the indiscriminate use of anti-infectives, and insist that antibiotics are not effective in the treatment of viral infections or illnesses such as the common cold. However, many patients demand prescriptions for these drugs when they visit practitioners because they are convinced that they need to take something to feel better.

With many serious illnesses, including pneumonias for which the causative organism is suspected, antibiotic therapy may be started as soon as a sample of the bacteria, or culture, is taken and before the results are known. In many cases, it is necessary to perform sensitivity testing on the cultured microbes to evaluate bacteria and determine which drugs are most effective. Health care providers also tend to try newly introduced, more powerful drugs when a more established drug may be just as effective. Use of a powerful drug in this way leads to the rapid emergence of resistant strains to that drug, perhaps limiting its potential usefulness when it might be truly necessary.

Self-assessment 2.3

1) Differentiate acquired resistance from natural resistance.
2) List 2 factors that can accelerate the occurrence of antibiotic resistance.
3) Around-the-clock dosing exposes people to the occurrence of antibiotic resistance. True or False

2.4. Classification of antibiotics with focus on antibiotics available in healthcare settings in Rwanda

Learning Activity 2.4

1) Observe attentively the image below:

a) Write the names of antibiotic drugs observed in the image above.

b) Put the drugs you identified in their respective classes.

c) What are the common side effects of antibiotics?

CONTENT SUMMARY

Bacteria can invade the human body through many routes. The goal of antibiotic therapy is to decrease the population of invading bacteria to a point at which the human immune system can effectively deal with the invader. To determine which antibiotic will effectively interfere with the specific proteins or enzyme systems for treatment of a specific infection, the causative organism must be identified through a culture. Sensitivity testing is also done to determine the antibiotic to which that particular organism is most sensitive (e.g., which antibiotic best kills or controls the bacteria). Drugs with broad spectrum activity are often given at the beginning of treatment until the exact organism and sensitivity can be established. Because

these antibiotics have such a wide range of effects, they are frequently associated with adverse effects. Human cells have many of the same properties as bacterial cells and can be affected in much the same way, so damage may occur to the human cells, as well as to the bacterial cells. There is no perfect antibiotic that is without effect on the human host.

Certain antibiotics may be contraindicated in some patients because of known adverse effects. Some patients for which antibiotics are contraindicated due to known adverse reactions include: Immunocompromised patients; Patients with severe GI disease, and Patients who are debilitated.

The antibiotic of choice is one that affects the causative organism and leads to the fewest adverse effects for the patient involved. In some cases, antibiotics are given in combination because they are synergistic. Use of synergistic antibiotics also allows the patient to take a lower dose of each antibiotic to achieve the desired effect. This helps to reduce the adverse effects that a particular drug may have. In some situations, antibiotics are used as a means of prophylaxis, or prevention of potential infection.

The most common side effects of antibiotics are: Ocular damage, superinfections (GI and genito-urinary tract), allergic reactions, bone marrow depression, GI effects, dermatological reactions, auditory damage and renal damage.

There are some pieces of advice, any patient taking antibiotics should follow: (1) Do not demand an antibiotic when you come to see your doctor. (2) Take your antibiotics as prescribed and use all pills even if you are feeling better. When you stop taking the pills before you have used them all, there's a likely chance that all of the bacteria have not been killed and the remaining bacteria will become stronger and replicate new bacteria that will be more resistant to the antibiotic next time around. (3) There should not be leftovers, and if for some reason there are, do not save them to take at another time. (4) Never share your antibiotics with someone else. (5) Always take antibiotics with food to prevent stomach upset, except otherwise indicated. (6) If the antibiotic is making you feel worse, talk to your doctor about your symptoms. You may need a different antibiotic or something that will help with the side effects. (7) Diarrhea is a common side effect of antibiotics. As a preventive measure, you can take an over-the-counter probiotic to help reduce diarrhea symptoms.

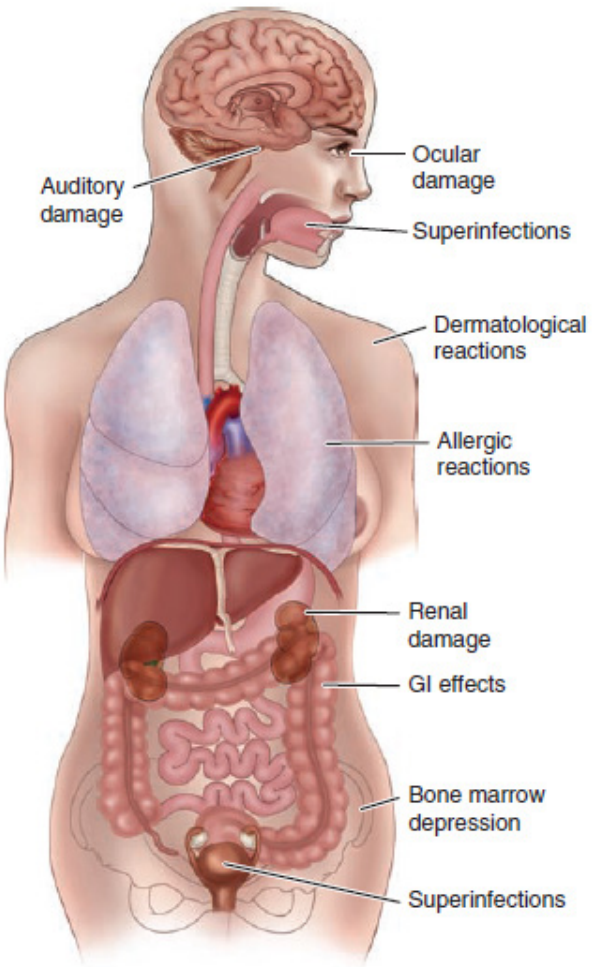


Image on common side effects of antibiotics

Antibiotics are classified into the following classes: Aminoglycosides, carbapenems, cephalosporins, fluoroquinolones, penicillins (and penicillinase-resistant drugs), sulfonamides, tetracyclines, disease-specific antimycobacterials (antitubercular and leprostatic drugs), ketolides (E.g.: telithromycin), lincosamides, lipoglycopeptides (E.g.: televancin), macrolides, and monobactams (E.g.: aztreonam).

Self-assessment 2.4

1) What is the advantage of using synergistic drugs?
2) Use of synergistic antibiotics allows the patient to increase the dose of each antibiotic to get the desired effect. True or False.

2.5 Class of penicillins and penicillinase resistant antibiotics

Learning Activity 2.5

1) Read the case study below and answer the questions related to it:

A 40-year-old female patient consults the health post where you are appointed in the clinical placement. She reports that she had unprotected sex, and developed a painless sore that disappeared after some period. You suspect that the patient suffers from syphilis, and you want to prescribe a drug in the class of penicillins.

a) Is it relevant to treat syphilis with drugs in the class of penicillins?

b) Give at least 5 drugs in the class of penicillins

c) Is is advisable to combine penicillins and parenteral aminoglycosides? Explain your answer.

CONTENT SUMMARY

Penicillin was the first antibiotic introduced for clinical use. Penicillins include penicillin G benzathine, penicillin G potassium, penicillin G procaine, penicillin V, amoxicillin, and ampicillin.

With the prolonged use of penicillin, more and more bacterial species have synthesized the enzyme penicillinase to counteract the effects of penicillin. A group of drugs with a resistance to penicillinase was developed, and this allows them to remain effective against bacteria that are now resistant to the penicillins. Penicillin-resistant antibiotics include nafcillin and oxacillin.

These antibiotics produce bactericidal effects by interfering with the ability of susceptible bacteria to build their cell walls when they are dividing. Because human cells do not use the biochemical process that the bacteria use to form the cell wall, this effect is a selective toxicity. The penicillins are indicated for the treatment of streptococcal infections, including pharyngitis, tonsillitis, scarlet fever, and endocarditis; pneumococcal infections; staphylococcal infections; fusospirochetal infections; rat-bite fever; diphtheria; anthrax; syphilis; and uncomplicatedgonococcal infections. At high doses, these drugs are also used to treat meningococcal meningitis.

Most of the penicillins are rapidly absorbed from the GI tract, reaching peak levels in 1 hour. Should be taken on an empty stomach to ensure adequate absorption. Penicillins are excreted unchanged in the urine, and enter breast milk which can cause adverse reactions.

Penicillins are contraindicated in patients with allergies to penicillin or cephalosporins or other allergens. Penicillin sensitivity tests are available if the patient's history of allergy is unclear and a penicillin is the drug of choice. Use with caution in patients with renal disease, in pregnant and lactating patients because diarrhea and superinfections may occur in the infant. Perform culture and sensitivity before therapy to select the right drug to the causal agent. With the emergence of many resistant strains of bacteria, this has become increasingly important.

GI adverse effects are common and include nausea, vomiting, diarrhea, abdominal pain, glossitis, stomatitis, gastritis, sore of the mouth, and furry tongue. Superinfections, including yeast may also develop. Pain and inflammation at the injection site can occur with injectable forms. Hypersensitivity reactions may include rash, fever, wheezing, and, with repeated exposure, anaphylaxis that can progress to anaphylactic shock and death.

Different drugs may interact with penicillins, and necessary precautions should be taken. If penicillins and penicillinase-resistant antibiotics are taken concurrently with tetracyclines, a decrease in the effectiveness of the penicillins results. This combination should be avoided if at all possible, or the penicillin doses should be raised, which could increase the occurrence of adverse effects. When the parenteral forms of penicillins and penicillinase-resistant drugs are administered in combination with any of the parenteral aminoglycosides, inactivation of the aminoglycosides occurs. These combinations should also be avoided whenever possible.

There is a variety of nursing considerations that need to be taken into account while administering the penicillins: Assess for possible contraindications or cautions; Perform a physical assessment to establish baseline data for evaluating the effectiveness of the drug and the occurrence of any adverse effects associated with drug therapy; Examine skin and mucous membranes for any rashes or lesions and injection sites for abscess formation to provide a baseline for possible adverse effects; Perform culture and sensitivity tests at the site of infection to ensure that this is the drug of choice for this patient; Note respiratory status to provide a baseline for the occurrence of hypersensitivity reactions; Examine the abdomen to monitor for adverse effects.

Tables 2.4.2.1: Summary of the prototype penicillins

	Amoxicillin:
Mechanism of action:	Inhibits synthesis of the cell wall in susceptible bacteria, causing cell death.
Indications:	Infections of the Ear, Nose, And Throat; Infections of the genitourinary tract; Infections of the skin and skin structure; Infections of the lower respiratory tract; Post-exposure prophylaxis for anthrax, treatment of Helicobacter infections as part of combination therapy and other susceptible strains.
Contraindications	Amoxicillin is contraindicated in patients who have experienced a serious hypersensitivity reaction (e.g.: anaphylaxis or Stevens-Johnson syndrome) to amoxicillin or to other β-lactam antibiotics (e.g., penicillins and cephalosporins).
Adverse effects	Hives, difficulty breathing, swelling of your face, lips, tongue, or throat, fever, sore throat, burning eyes, skin pain, red or purple skin rash with blistering and peeling, severe stomach pain, and diarrhea that is watery or bloody (even if it occurs months after the last dose), nausea, vomiting, diarrhea, and rash.
Dosage and route:	**Dosage and route: Dosage:** 25-45 mg/kg/day in divided doses **Route:** Oral
Dosage form:	**Dosage form:** Capsules or tablets, and oral suspension

	Ampicillin
Mechanism of action:	Exerts bactericidal activity via inhibition of bacterial cell wall synthesis by binding one or more of the penicillin binding proteins.
Indications:	Treatment of susceptible bacterial infections (nonbeta-lactamase-producing organisms); treatment or prophylaxis of infective endocarditis; susceptible bacterial infections caused by streptococci, pneumococci, nonpenicillinase-producing staphylococci, Listeria, meningococci; some strains of H. influenzae.
Contraindications	Hypersensitivity to ampicillin or other penicillins , Cephalosporin hypersensitivity
Precautions:	Cephalosporin hypersensitivity

Adverse effects	Fever, penicillin encephalopathy, seizure, Erythema multiforme, exfoliative dermatitis, rash, urticarial, Black hairy tongue, diarrhea, pseudomembranous colitis, sore mouth or tongue, stomatitis, vomiting
Dosage and route:	**Dosage range:** Oral: 250-500 mg every 6 hours Injection: I.M., I.V.: 1-2 g every 4-6 hours or 50-250 mg/kg/day in divided doses (maximum: 12 g/day)
Dosage form:	Injection form, capsules, oral suspension

	Cloxacillin
Mechanism of action:	Exerts bactericidal activity via inhibition of bacterial cell wall synthesis by binding one or more of the penicillin binding proteins.
Indications:	The treatment of beta-hemolytic streptococcal and pneumococcal infections as well as staphylococcal infections (including those caused by beta-lactamase producing organisms). In severe staphylococcal infections (septicaemia, osteomyelitis, endocarditis, pneumonia) or when staphylococci are suspected.
Contraindications	It is contraindicated in patients who are hypersensitive to this drug, to penicillin, or to cephalosporins or to any component of the container.
Precautions:	It may be expected the most common untoward reactions will be related to sensitivity.
Adverse effects	Adverse reactions are in different categories: **Gastrointestinal effects:** Nausea, vomiting, epigastric discomfort, flatulence and loose stools have been noted in some patients **Hematologic effects:** Eosinophilia, leucopenia, anemia, thrombocytopenia, thrombocytopenic, purpura, neutropenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Thrombophlebitis has occurred during the course of i.v. therapy. Mildly elevated SGOT level (less than 100 units) have been reported. **Immune effects:** Allergic reactions (rash, urticaria) including wheezing and sneezing have been reported.

Dosage and route:	**Dosage and route:** Dosage range: Oral: 250-500 mg every 6 hours Injection: I.M., I.V.: 1-2 g every 4-6 hours or 50-250 mg/kg/day in divided doses (maximum: 12 g/day)
Dosage form:	**Dosage form:** Injection form, capsules, oral suspension

	Penicillin V
Mechanism of action:	Penicillin V exerts a bactericidal action against penicillin-sensitive microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall mucopeptide.
Indications:	Streptococcal upper respiratory tract infections, scarlet fever, and erysipelas infections, Pneumococcal upper respiratory infections, Staphylococcal skin and soft tissue infections, Fusospirochetosis (infection of the oropharynx or middle part of the throat) and prevention of rheumatic fever.
Contraindications	Anaphylactic reactions to beta-lactams
Adverse effects	Nausea, vomiting, stomach upset, diarrhea, black hairy tongue, allergic reactions.
Dosage and route:	**Adult dosage (ages 18 years and older): Typical dosage:** 125–250 mg taken every 6–8 hours for 10 days.The dosage may go up to 500 mg taken every 6–8 hours. **Child dosage (ages 12–17 years): Typical dosage:** 125–250 mg taken every 6–8 hours for 10 days.
Dosage form:	Tablets for oral use

	Penicillin G procaine
Mechanism of action:	Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall peptidoglycan, rendering the cell wall osmotically unstable

Indications:	Pneumonia, Streptococcal infections (Group A), Staphylococcal infections, Bacterial endocarditis, Syphilis, Anthrax, Diphtheria
Contraindications	Hypersensitivity; serious and occasionally fatal reactions have been reported.
Adverse effects	Skin rashes including maculopapular eruptions and exfoliative dermatitis; UrticariaSerum-sickness like reactions (eg, chills, fever, edema, arthralgia, prostration);Jarisch-Herxheimer reaction reported when treating syphilis; andPseudomembranous colitis.
Dosage and route:	600,000-2.4 million units IM q Day depending on the severity. The dose may be as low as 300,000 units, and the duration can range between 7 and 14 days.
Dosage form:	Vials with powder for injection

	Penicillin G benzathine
Mechanism of action:	Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall peptidoglycan, rendering the cell wall osmotically unstable
Indications:	Pneumonia, Streptococcal infections (Group A), Staphylococcal infections, Bacterial endocarditis, Syphilis, Anthrax, Diphtheria.
Contraindications:	Hypersensitivity; serious and occasionally fatal reactions have been reported.
Contraindications:	Hypersensitivity; serious and occasionally fatal reactions have been reported.
Adverse effects:	Skin rashes including maculopapular eruptions and exfoliative dermatitis;Urticaria, Serum-sickness like reactions (eg, chills, fever, edema, arthralgia, prostration);Jarisch-Herxheimer reaction reported when treating syphilis; and Pseudomembranous colitis.
Dosage and route:	1,200,000-2.4 million units IM every week or 2 weeks depending on the severity.
Dosage form:	Vials with powder for injection.

Self-assessment 2.5

1) Which of the following statements describes the mechanism of action of amoxicillin?
   a) Interference with the 50S subunit of bacterial ribosomes
   b) Inhibition of bacterial cell wall synthesis
   c) Interference with the 30S subunit of bacterial ribosomes
   d) Suppression of folate synthesis
2) One of the following penicillin drugs is effective on infections caused by beta-lactamase producing organisms:
   a) Cloxacillin
   b) Amoxicillin
   c) Ampicillin
   d) Penicillin V
3) One of the following penicillin antibiotics can be used in the prophylaxis of rheumatic fever and syphilis:
   a) Amoxicillin
   b) Ampicillin
   c) Penicillin V
   d) Penicillin G benzathine
4) The healthcare professionals need to take necessary caution when administering penicillins to people allergic to cephalosporins. True or False

2.6 Class of aminoglycosides

Learning Activity 2.6

1) Read the case study below and answer the questions related to it:

A 50-year-old male patient consults the health post where you are carrying out the clinical placement. He has a serious bacterial infectious disease that requires treatment with an aminoglycoside. You then refer the patient to the nearest district hospital to receive an aminoglycoside through the parenteral route. Answer the following questions related to the scenario above:

a) Give at least 3 drugs in the class of aminoglycosides

b) Which mechanism of action do aminoglycosides use to exert their effects?

Guidance: Read the textbook provided by the teacher, on the topic of aminoglycosides, and answer the questions above.

CONTENT SUMMARY

Aminoglycosides are powerful antibiotics used to treat serious infections caused by gram-negative aerobic bacilli. Because most of these drugs have potentially serious adverse effects, newer, less-toxic drugs have replaced aminoglycosides in the treatment of less serious infections. They include amikacin (Amikin), gentamicin (Garamycin), Kanamycin (Kantrex), neomycin (Mycifradin), streptomycin, and tobramycin (TOBI, Tobrex),promomycin and plazomycin.

The aminoglycosides are bactericidal and inhibit protein synthesis in susceptible strains of gram-negative bacteria. These antibiotics are used to treat serious infections caused by Pseudomonas aeruginosa, E. coli, Proteus species, the Klebsiella, Enterobacter, Serratia group, Citrobacter species, and Staphylococcus species such as Staphylococcus aureus.

Aminoglycosides are broad-spectrum antibiotics. Th e toxic potential of these drugs limits their use. Since their introduction into clinical use 50 years ago, aminoglycosides continue to play an important role in the treatment of severe infections. Major aminoglycosides include amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, and tobramycin.

Mechanism of Action

Aminoglycosides are bactericidal; they inhibit bacterial protein synthesis, causing cell death. Th eir mechanism of action is not fully known.

Indications

Aminoglycosides are prescribed for a variety of disorders and infectious diseases.

Streptomycin: Th is can be used to treat tularemia, acute brucellosis, bacterial endocarditis, tuberculosis, and plague.

Amikacin, gentamycin, netilmicin, and tobramycin: These are prescribed for serious Gram-negative bacillary infections such as Enterobacter, klebsiella, bacteremia, meningitis, and peritonitis.

Neomycin: Th is used for pre-operative bowel sterilization, hepatic coma, and in topical form for burns.

Cautions should be taken while using during pregnancy (the benefits of the drug must be carefully weighed against potential adverse effects on the fetus).

Test urine function frequently when these drugs are used because they depend on the kidney for excretion and are toxic to the kidney. The potential for nephrotoxicity and ototoxicity with amikacin is very high with the use of aminoglycosides, and special caution for kanamycin is to ensure it is not used for longer than 7 to 10 days. Streptomycin, once a commonly used drug, is reserved for use in special situations because it is very toxic to the eighth cranial nerve and kidney.

Their main severe side effects may include ototoxicity, nephrotoxicity, and neuromuscular blockade. The interaction of aminoglycoside antibiotics and calcium channel blockers is of clinical significance because when these agents are given concurrently during the perioperative period they may lead to respiratory depression or prolonged apnoea.

There are some nursing considerations that need to be taken into account while administering aminoglycosides. Assess for possible contraindications or cautions. Perform a physical assessment to establish baseline data for assessing the effectiveness of the drug and the occurrence of any adverse effects associated with drug therapy. Perform culture and sensitivity tests at the site of infection to ensure appropriate use of the drug. Conduct auditory testing to evaluate any CNS effects of the drug, perform renal and hepatic function tests, and assess vital signs.

Tables 2.4.3.1: Summary of the prototype aminoglycosides

Aminoglycoside	Trade Name	Route of Administration	Common Dosage Range	Spectrum of Activity	Adverse Effects
Streptomycin	generic only	IM	15 mg/kg up to 1 g/d as a single dose	Mycobacterium tuberculosis, some Gram-negative bacteria	Ototoxicity, nephrotoxicity
Gentamicin	Garamycin®	IM, IV	1.5–2.0 mg/kg/day (standard dose)	Broad, Gram-negative, Pseudomonas aeruginosa	Ototoxicity, nephrotoxicity
Tobramycin	Tobrex®	IM, IV	3 mg/kg t.i.d.	Potent against Pseudomonas aeruginosa,cystic fibrosis	Ototoxicity (auditory), nephrotoxicity
Amikacin	Amikin®	IM, IV	5–7.5 mg/kg/day in 2–3 divided doses	Multidrug-resistant Gram-negative bacteria	Ototoxicity, nephrotoxicity
Neomycin sulfate	Mycifradin®	PO, IM, Topical	PO: 50 mg/kg in 4 div. doses for 2–3 days; IM: 1.3–2.6 mg/kg q.i.d.; Topical: apply 1–3 times/ day	Broad, primarily used topically	High nephrotoxicity, ototoxicity
Kanamycin	Kantrex® 1	IM, IV	5 mg/kg each 8–12 hours	For serious infections	Nephrotoxicity (Kidney Damage), Ototoxicity, neuromuscular blockade, leading to muscle weakness, Allergic Reactions, Gastrointestinal Disturbances, Pain, swelling

Self-assessment 2.6

1. How do aminoglycosides inhibit protein synthesis in gram-negative bacteria, and what makes them bactericidal?
2. a. In what scenarios are aminoglycosides preferred over penicillin for treating serious infections, and why are they used when penicillin is contraindicated?
   b. Why might aminoglycosides be chosen for empirical treatment before culture and sensitivity results are available?
3. a. How does the rapid absorption of aminoglycosides after intramuscular injection influence their use in clinical practice?
   b. What are the implications of aminoglycosides crossing the placenta and entering breast milk for pregnant or breastfeeding patients?
4. What are the common gram-negative bacteria that aminoglycosides are effective against, and how do they compare in terms of effectiveness against these pathogens?
5. a. What are the major adverse effects associated with aminoglycosides, and how do these risks influence their clinical use?
   b. why are aminoglycosides contraindicated in patients with renal or hepatic?

2.7 Class of cephalosporins

Learning Activity 2.7

1) Read the scenario below:

A 18-year-old male patient comes to the health facility with compalins of chronic wound drainage, pain, and exposed bone. On the observation, the patient is suspected to have a chronic osteomyelitis, and he is sheduled for surgery. Postoperatively, the patient is written a third generation cephalosporin for 14 days. Answer the following questions related to the case study above

a) Give at least 2 drugs in the class of third generation cephalosporins

b) Which mechanism of action do cephalosporins use to exert their effects?

CONTENT SUMMARY

The cephalosporins are drugs similar to the penicillins in structure and in activity. This means that their mechanism of action is through **inhibition of bacterial cell wall peptidoglycan synthesis**.

Over time, different generations of cephalosporins have been introduced, each group with its own spectrum of activity. In this book, only 3 generations will be discussed.

First-generation cephalosporins are largely effective against the same gram-positive bacteria that are affected by penicillin G, as well as the gram-negative bacteria P. mirabilis, E. coli, and K. pneumoniae. First-generation drugs include cefadroxil (generic), cefazolin (Zolicef), and cephalex.

Second-generation cephalosporins are effective against the previously mentioned strains, as well as H. influenzae, Enterobacter aerogenes, and Neisseria species. Second-generation drugs are less effective against gram-positive bacteria. These include cefaclor (Ceclor), cefoxitin (generic), cefprozil (generic), and cefuroxime (Zinacef).

Third-generation cephalosporins, which are effective against all of the previously mentioned strains, are weak against gram-positive bacteria but are more potent against the gram-negative bacilli. Third-generation drugs include cefdinir (Omnicef), cefotaxime (Claforan), cefpodoxime (Vantin), ceftazidime (Ceptaz, Tazicef), ceftibuten (Cedax), ceftizoxime (Cefi zox), and ceftriaxone (Rocephin).

The cephalosporins are both bactericidal and bacteriostatic, depending on the dose used and the specific drug involved. In susceptible species, these agents basically interfere with the cell wall–building ability of bacteria when they divide; that is, they prevent the bacteria from biosynthesizing the framework of their cell walls.

Avoid the use of cephalosporins in patients with known allergies to cephalosporins or penicillins because cross-sensitivity is common. Use with caution in patients with hepatic or renal impairment because these drugs are toxic to the kidneys and could interfere with the metabolism and excretion of the drug. In addition, use with caution in pregnant or lactating patients because potential effects on the fetus and infant are not known; use only if the benefits clearly outweigh the potential risk of toxicity to the fetus or infant.

The most common adverse effects of the cephalosporins involve the GI tract and include nausea, vomiting, diarrhea, anorexia, abdominal pain, and flatulence. CNS symptoms include headache, dizziness, lethargy, and paresthesias. Nephrotoxicity is also associated with the use of cephalosporins, most particularly in patients who have a predisposing renal insufficiency

Patients who receive oral anticoagulants in addition to cephalosporins may experience increased bleeding. Instruct the patient receiving cephalosporins to avoid alcohol for up to 72 hours after discontinuation of the drug to prevent a disulfiram-like reaction, which results in unpleasant symptoms such as flushing, throbbing headache, nausea and vomiting, chest pain, palpitations, dyspnea, syncope, vertigo, blurred vision, and, in extreme reactions, cardiovascular collapse,

convulsions, or even death. Concurrent administration of cephalosporins with aminoglycosides increases the risk for nephrotoxicity. Frequently monitor patients receiving this combination, and evaluate serum blood urea nitrogen (BUN) and creatinine levels.

There is a variety of nursing considerations that need to be taken into account: Assess for possible contraindications or cautions. Monitor the patient for any signs of superinfection to arrange for treatment if superinfection occurs. Instruct the patient about the appropriate dosage schedule and about possible side effects to enhance patient knowledge about drug therapy and to promote compliance. Take safety precautions, including changing position slowly and avoiding driving and hazardous tasks, if CNS effects occur. Try to drink a lot of fluids and to maintain nutrition (very important) even though nausea, vomiting, and diarrhea may occur. Report difficulty breathing, severe headache, severe diarrhea, dizziness, or weakness. Avoid consuming alcoholic beverages while receiving cephalosporins and for at least 72 hours after completing the drug course because serious side effects could occur.

Tables. 2.7 Summary the prototype cephalosporins

CEPHALOSPORINS OF FIRST GENERATION:

	Cefadroxil
Mechanism of action:	Inhibits bacterial wall synthesis.
Indications:	Skin or Soft Tissue Infection, Tonsillitis, Pharyngitis, Cystitis, Pyelonephritis, Urinary Tract Infection, and Osteomyelitis.
Contraindications	You should not take this medicine if you are allergic to cefadroxil or other cephalosporin antibiotic (cefdinir, cefalexin, Keflex, Omnicef, and others).
Adverse effects	stomach upset or pain, nausea, vomiting, diarrhea, stiff or tight muscles, joint pain, feeling restless or hyperactive, unusual or unpleasant taste in your mouth, itching or skin rash, or vaginal itching or discharge.
Dosage and route:	Route: Oral Dosage:1 gram once a day OR in divided doses given 2 times a day for 10 days
Dosage form:	Oral Suspension

	Cefazolin
Mechanism of action:	Inhibition of bacterial cell wall peptidoglycan synthesis
Indications:	Urinary tract infections caused by E. coli; P. mirabilis, and Klebsiella species. Skin and skin structure infections caused by staphylococci and/or streptococci. Pharyngitis and/or tonsillitis caused by Streptococcus pyogenes (Group A beta-hemolytic streptococci).
Contraindications	Cefazolin for injection is contraindicated in patients who have a history of immediate hypersensitivity reactions to cefazolin or the cephalosporin class of antibacterial drugs, penicillins, or other beta-lactams
Adverse effects	• Genital itching, white patches in mouth, loss of appetite. • Heartburn, nausea, vomiting, and diarrhea.
Dosage and route:	250 to 500 mg IV or IM every 8 hours for 6 weeks
Dosage form:	Powder for injection.

CEPHALOSPORINS OF SECOND GENERATION

	Cefoxitin
Mechanism of action:	Acts by inhibition of bacterial cell wall synthesis.
Indications:	• Lower respiratory tract infections • Urinary tract infections • Intra-abdominal infections • Gynecological infections • Septicemia • Bone and joint infections • Skin and skin structure infections
Contraindications	The following conditions are contraindicated with this drug: Diarrhea from an infection with Clostridium difficile bacteria,Inflammation of the large intestine,decreased kidney function

Adverse effects	Swelling, redness, pain, or soreness at the injection site may occur. This medication may also rarely cause loss of appetite, nausea, vomiting, diarrhea, or
Dosage and route:	The usual adult dosage range is 1 gram to 2 grams every 6 to 8 hours Duration: 10 days
Dosage form:	Injection

	Cefuroxime
Mechanism of action:	Acts by inhibition of bacterial cell wall synthesis
Indications:	**Cefuroxime** is indicated for the treatment of a variety of infections including acute bacterial otitis media, several upper respiratory tract infections, skin infections, urinary tract infections, gonorrhea, early Lyme disease, and impetigo.
Contraindications	The following conditions are contraindicated with this drug: Diarrhea from an infection with Clostridium difficile bacteria,a decrease in the blood clotting protein prothrombin, chronic kidney disease stage 4 (severe) and chronic kidney disease stage 5 (failure).
Adverse effects	• Nausea, vomiting, diarrhea, or stomach pain may occur. • Dizziness and drowsiness may occur less frequently, especially with higher doses
Dosage and route:	Adults and teenagers—250 to 500 milligrams (mg) two times a day for 10 days. Children (who can swallow the tablets)—250 mg two times a day for 10 days
Dosage form:	film-coated tablets Suspension

CEPHALOSPORINS OF THIRD GENERATION

	Ceftriaxone
Mechanism of action:	Inhibiting the mucopeptide synthesis in the bacterial cell wall.
Indications:	Used for the treatment of the infections (respiratory, skin, soft tissue, UTI, ENT) caused by susceptible organisms.
Contraindications	The following conditions are contraindicated with this drug: diarrhea from an infection with Clostridium difficile bacteria, hemolytic anemia, liver problems, disease of the gallbladder, severe renal impairment, yellowing of the skin in a newborn child
Adverse effects	Common side effects of Ceftriaxone include: rash, diarrhea, nausea, • vomiting, upset stomach, blood clots,dizziness, headache
Dosage and route:	Parenteral IM:1G/3.5ML Parenteral IV: 1 or 2G/10ML Duration: 10 to 14 days
Dosage form:	Injection

	Cefotaxime
Mechanism of action:	Inhibit bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins
Indications:	• For the treatment of bacteraemia and sepsis. • For the treatment of bacterial meningitis and ventriculitis. • For the treatment of gonorrhoea.
Contraindications	Cefotaxime is contraindicated in patients with cephalosporin hypersensitivity or cephamycin hypersensitivity. Cefotaxime should be used cautiously in patients with hypersensitivity to penicillin.
Adverse effects	injection site reactions (pain, irritation, a hard lump, or inflammation),rash, itching, fever, nausea, vomiting, Stomach pain, Headaches, diarrhea, vaginal itching or discharge, and colitis
Dosage and route:	Parenteral IM: 1 g IM once IV: 1-2 g IV Duration: 10 to 14 days
Dosage form:	injection

Self-assessment 2.7

1) Which of the following antibiotics belongs to the class of cephalosporins?

a) Amoxicillin

b) Gentamicin

c) Cefotaxime

d) Bactrim

2) Which of the following IS NOT a caution for the use of cephalosporins?

a) Allergy to penicillin

b) Allergy to aspirin

c) Renal failure

d) Concurrent treatment with aminoglycosides

2.8. Class of fluoroquinolones

Learning Activity 2.8

1) Read the scenario below:

A 30-year-old female patient consults the health post where you allocated during the clinical practice, complaining of recurrent urinary tract infections on a pregnancy of 3 months. The patient reports that he was treated with amoxicillin without success. You then decide to prescribe a fluoroquinolone antibiotic, bearing in mind its effectiveness in urinary tract infections.

a) List at least 4 fluoroquinolone drugs

b) Bearing in mind that this patient is pregnant, is it advisable to prescribe fluoroquinolones?

Guidance: Read the textbook provided by the teacher, on the topic of fluoroquinolones, and answer the questions above.

CONTENT SUMMARY

The fluoroquinolones are a relatively new synthetic class of antibiotics with a broad spectrum of activity. Fluoroquinolones include ciprofloxacin (Cipro), which is the most widely used fluoroquinolone; gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), and ofloxacin.

The fluoroquinolones enter the bacterial cell by passive diffusion through channels in the cell membrane. Once inside, they interfere with the action of DNA enzymes necessary for the growth and reproduction of the bacteria. This leads to cell death because the bacterial DNA is damaged and the cell cannot be maintained. However, misuse of these drugs in the short time the class has been available has led to the existence of resistant strains of bacteria.

The fluoroquinolones are indicated for treating infections caused by susceptible strains of gram-negative bacteria, S. aureus, Staphylococcus epidermidis, some Neisseria gonorrhoeae, and group D streptococci. These infections frequently include urinary tract, respiratory tract, and skin infections. Ciprofloxacin is effective against a wide spectrum of gram-negative bacteria.

Fluoroquinolones are contraindicated in patients with known allergy to any fluoroquinolone and in pregnant or lactating patients because potential effects on the fetus and infant are not known. Use with caution in the presence of renal dysfunction, which could interfere with the metabolism and excretion of the drug, and seizures, which could be exacerbated by the drugs' effects on cell membrane channels. The use of antacids has been recognized to impair the action of fluoroquinolones, therefore, such concomitant use is not recommended.

These drugs are generally associated with relatively mild adverse reactions. The most common are headache, dizziness, insomnia, and depression related to possible effects on the CNS membranes. GI effects include nausea, vomiting, diarrhea, and dry mouth, related to direct drug effect on the GI tract and possibly to stimulation of the chemoreceptor trigger zone in the CNS.

There are nursing considerations that the nurses ought to bear in mind: Assess for possible contraindications or cautions. Perform physical assessment to establish baseline data for assessing the effectiveness of the drug and the occurrence of any adverse effects associated with drug therapy. Examine the skin for any rash or lesions to provide a baseline for possible adverse effects. Perform culture and sensitivity tests at the site of infection to ensure appropriate use of the drug. Perform renal function tests, including blood urea nitrogen and creatinine clearance, to evaluate the status of renal functioning and to assess necessary changes in dose. Conduct assessment of orientation, affect, and reflexes to establish a baseline for any central nervous system (CNS) effects of the drug.

Table 2.4.5.1: Summary of the prototype fluoroquinolones

	Ciprofloxacin
Mechanism of action:	The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination
Indications:	Bone and joint infections, complicated intra-abdominal infections, infectious diarrhea, typhoid Fever (Enteric Fever), uncomplicated cervical and urethral, gonorrhoea, chronic bacterial
Contraindications	Hypersensitivity: Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antibacterial, or any of the product components Ciprofloxacin should not be used
Adverse effects	• Diarrhea, dizziness, headache, stomach upset, abdominal pain, nausea/vomiting, and rash
Dosage and route:	Usual oral dose in adults is 250-750 mg (immediate release tablets) every 12 hours or 500-1000 mg (extended release tablets) every 24 hours.
Dosage form:	Infusion solution Oral suspension Oral tablets

	Levofloxacin
Mechanism of action:	Levofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria.it functions by inhibiting the DNA gyrase and topoisomerase IV, two bacterial type II topoisomerases
Indications:	Community-Acquired Pneumonia, Skin infections, Chronic Bacterial Prostatitis, Plague, Urinary Tract Infections, Acute Pyelonephritis, Acute bacterial exacerbation of chronic bronchitis
Contraindications	The following conditions are contraindicated with this drug: diarrhoea from an infection with Clostridium difficile bacteria, diabetes, low blood sugar, and slow heartbeat.

Adverse effects	Headache, sweating,irritability, dizziness, nausea, fast heart rate, feeling anxious or shaky, numbness or tingling in your hands, arms, legs or feet, weakness in your arms, hands, legs or feet, burning pain in your
Dosage and route:	Common side effects of Levaquin include: Nausea, vomiting,diarrhea, headache,constipation, difficulty sleeping (insomnia), dizziness, abdominal pain.
Dosage form:	Injection, oral solution, tablet.

Self-assessment 2.8

1) Read the scenario below:

A 32-year-old female patient consults the health post where you are appointed, complaining of recurrent urinary tract infections. The patient reports that he was treated with amoxicillin without success. You then decide to prescribe a fluoroquinolone antibiotic, bearing in mind its effectiveness in urinary tract infections.

a) What are the nursing considerations you would consider before prescribing a fluoroquinolone to any patient?

2.9 Class of macrolides

Learning Activity 2.9

1) Read the scenario below:

You receive a 60-year-old male patient who consults the health post where you work with complaints of respiratory tract infection. The patient reports that he took amoxicillin in the past, and developed an allergic reaction. He was then warned not to take any penicillin drug again in the past, because of allergy to penicillins. You then decide to prescribe a macrolide antibiotic, as it may replace a penicillin in such infections.

a) List at least 2 antibiotics that belong to the class of macrolides

b) What is the mechanism of action of a macrolide?

CONTENT SUMMARY

The macrolides are antibiotics that interfere with protein synthesis in susceptible bacteria. Macrolides include erythromycin, azithromycin, clarithromycin, and dirithromycin.

The macrolides may be bactericidal or bacteriostatic, exerting their effect by binding to the bacterial cell membrane and changing protein function. This action can prevent the cell from dividing or cause cell death, depending on the sensitivity of the bacteria and the concentration of the drug.

Macrolides are indicated for treatment of the following conditions: acute infections caused by susceptible strains of S. pneumoniae, M. pneumoniae, Listeria monocytogenes, and Legionella pneumophila; infections caused by group A beta-hemolytic streptococci; pelvic inflammatory disease caused by N. gonorrhoeae; upper respiratory tract infections caused by H. influenzae (with sulfonamides); infections caused by Corynebacterium diphtheriae and Corynebacterium minutissimum (with antitoxin); intestinal amebiasis; and infections caused by C. trachomatis.

In addition, macrolides may be used as prophylaxis for endocarditis before dental procedures in high-risk patients with valvular heart disease who are allergic to penicillin. Topical macrolides are indicated for the treatment of ocular infections caused by susceptible organisms and for acne vulgaris, and they may also be used prophylactically against infection in minor skin abrasions and for the treatment of skin infections caused by sensitive organisms.

The macrolides are widely distributed throughout the body; they cross the placenta and enter the breast milk. These drugs are absorbed in the GI tract.

Erythromycin is metabolized in the liver, with excretion mainly in the bile to feces. The half-life of erythromycin is 1.6 hours.

Azithromycin and clarithromycin are mainly excreted unchanged in the urine, making it necessary to monitor renal function when patients are taking these drugs. The half-life of azithromycin is 68 hours, making it useful for patients who have trouble remembering to take pills because it can be given once a day. The half-life of clarithromycin is 3 to 7 hours. Dirithromycin is converted from the prodrug dirithromycin to erythromycylamine in the intestinal wall. Most of the drug is excreted through the feces. It has a half-life of 2 to 36 hours. It also has the advantage of once-a-day dosing, which increases compliance in many cases.

Macrolides are contraindicated in patients with a known allergy to any macrolide because cross-sensitivity occurs. Use with caution in patients with hepatic dysfunction, which could alter the metabolism of the drug, and in those with renal

disease, which could interfere with the excretion of some of the drug. Also use with caution in lactating women because macrolides secreted in breast milk can cause diarrhea and superinfections in the infant and in pregnant women because of potential adverse effects on the developing fetus; use only if the benefit clearly outweighs the risk to the fetus.

Relatively few adverse effects are associated with the macrolides. The most frequent ones, which involve the direct effects of the drug on the GI tract, are often uncomfortable enough to limit the use of the drug. These include abdominal cramping, anorexia, diarrhea, vomiting, and pseudomembranous colitis. Other effects include neurological symptoms such as confusion, abnormal thinking, and uncontrollable emotions, which could be related to drug effects on the CNS membranes; hypersensitivity reactions ranging from rash to anaphylaxis; and superinfections related to the loss of normal flora.

During macrolide administration, there are nursing considerations that nurses need to consider: GI upset is common and patients can be advised to take medication with food. Patients should also be advised to avoid excessive sunlight and to wear protective clothing and use sunscreen when outside, as well as to report any adverse reactions immediately. Advise patients to report symptoms of chest pain, palpitations, or yellowing of eyes or skin. Additionally, patients should be advised that these medications can cause drowsiness.

Assess for possible contraindications or precautions to macrolides. Perform a physical assessment to establish baseline data for assessing the effectiveness of the drug and the occurrence of any adverse effects associated with drug therapy. Examine the skin for any rash or lesions to provide a baseline for possible adverse effects. Obtain specimens for culture and sensitivity testing from the site of infection to ensure appropriate use of the drug. Monitor temperature to detect infection. Conduct assessment of orientation, affect, and reflexes to establish a baseline for any CNS effects of the drug. Assess liver and renal function test values to determine the status of renal and liver functioning and to determine any needed alteration in dosage.

Tables 2.9 Summarizing of the prototype macrolides

	Erythromycin
Mechanism of action:	Binds to cell membranes, causing a change in protein function and cell death; can be bacteriostatic or bactericidal.
Indications:	Treatment of respiratory, dermatological, urinary tract, and gastrointestinal infections caused by susceptible strains of bacteria.

Contraindications	Known hypersensitivity to erythromycin, patients taking terfenadine, astemizole, cisapride, pimozide, ergotamine, or dihydroergotamine.
Adverse effects	Abdominal cramping, vomiting, diarrhea, rash, superinfection, liver toxicity, risk for pseudomembranous colitis, potential for hearing loss.
Dosage and route:	Oral tables, oral suspension.
Dosage form:	**Adults:** 250 mg four times daily in equally spaced doses or 500 mg every 12 hours. Maximum: 4 g per day. **Children:** 30 to 50 mg/kg/day, in equally divided doses. Maximum: 4 g per day.

	Clarithromycin
Mechanism of action:	Inhibits bacterial protein synthesis by binding to the bacterial 50S ribosomal subunit.
Indications:	Acute otitis, pharyngitis, tonsillitis, respiratory tract infections, uncomplicated skin infections, and helicobacter pylori infection
Contraindications	Known hypersensitivity to the active substance clarithromycin, to other macrolides or to any of the excipients. Concomitant administration with astemizole, cisapride, pimozide, terfenadine, ergotamine or dihydroergotamine. Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
Adverse effects	Abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild. Insomnia, dysgeusia, headache, vasodilation, dyspepsia, abnormal liver function test, esophagitis, gastrooesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation, and flatulence may also develop.
Dosage and route:	Oral tablets, oral suspension.
Dosage form:	**Adults and adolescents (12 years and older):** 250 mg twice daily. Maximum: 500 mg twice daily in severe infections. Children under 12 years of age should use clarithromycin paediatric suspension

Self-assessment 2.9

1) Which of the following antibiotic would be given to a patient with gastritis associated with Helicobacter pylori?
   a) Erythromycin
   b) Clarithromycin
   c) Gentamicin
   d) Doxycycline
2) All of the following antibiotics are macrolides, **Except:**
   a) Erythromycin
   b) Clarithromycin
   c) Azithromycin
   d) Streptomycin

2.10 Class of tetracyclines

Learning Activity 2.10

1) Read the scenario below:

You receive a 45-year-old female patient who consults the health post where you are doing your clinical placement, with complaints of urinary tract infection. This infection can be treated by a tetracycline antibiotic that is effective against some bacteria that cause urinary tract infection. As a student nurse, you wish to prescribe a tetracycline antibiotic that will help to clear the infection.

a) List at least 2 antibiotics that belong to the class of tetracyclines
b) What is the mechanism of action of tetracyclines?

CONTENT SUMMARY

The class of tetracyclines has been developed as semisynthetic antibiotics basing on the structure of a common soil mold. They are composed of four rings, which defines how they got their name. Researchers have developed newer tetracyclines to increase absorption and tissue penetration. Their use has been limited in recent years due to their noted widespread resistance. Existing Tetracyclines include tetracycline (Sumycin), demeclocycline (Declomycin), doxycycline (Doryx, Periostat), and minocycline (Minocin).

The tetracyclines work by inhibiting protein synthesis in a wide range of bacteria, leading to the inability of the bacteria to multiply. Because the affected protein is similar to a protein found in human cells, these drugs can be toxic to humans at high concentrations.

Tetracyclines are indicated for treatment of infections caused by susceptible agents; when penicillin is contraindicated in susceptible infections; and for treatment of acne and uncomplicated GU infections caused by C. trachomatis. Some of the tetracyclines are also used as adjuncts in the treatment of certain protozoal infections such as malaria.

Tetracyclines are absorbed adequately, but not completely, from the GI tract. Their absorption is affected by food, iron, calcium, and other drugs in the stomach. Tetracyclines are concentrated in the liver and excreted unchanged in the urine, with half-lives ranging from 12 to 25 hours. These drugs cross the placenta and pass into breast milk. Tetracycline is available in oral and topical forms, in addition to being available as an ophthalmic agent. Demeclocycline is available in oral form. Doxycycline and minocycline are available in IV and oral forms.

Tetracyclines are contraindicated in patients with known allergy to tetracyclines or to tartrazine (e.g., in specifi c oral preparations that contain tartrazine) and during pregnancy and lactation because of effects on developing bones and teeth.

The ophthalmic preparation is contraindicated in patients who have fungal, mycobacterial, or viral ocular infections because the drug kills not only the undesired bacteria but also bacteria of the normal flora, which increases the risk for exacerbation of the ocular infection that is being treated. Tetracyclines should be used with caution in children younger than 8 years of age because they can potentially damage developing bones and teeth and in patients with hepatic or renal dysfunction because they are concentrated in the bile and excreted in the urine.

The major adverse effects of tetracycline therapy involve direct irritation of the GI tract and include nausea vomiting, diarrhea, abdominal pain, glossitis, and dysphagia. Fatal hepatotoxicity related to the drug's irritating effect on the liver has also been reported. Skeletal effects involve damage to the teeth and bones. Because tetracyclines have an affinity for teeth and bones, they accumulate there, weakening the structure and causing staining and pitting of teeth and bones. Dermatological effects include photosensitivity and rash. Superinfections, including yeast infections, occur when bacteria of the normal flora are destroyed. Local effects, such as pain and stinging with topical or ocular application, are fairly common. Hematological effects are less frequent, such as hemolytic anemia and bone marrow depression secondary to the effects on bone marrow cells that turn over rapidly. Hypersensitivity reactions reportedly range from urticaria to anaphylaxis and also include intracranial hypertension

When penicillin G and tetracyclines are taken concurrently, the effectiveness of penicillin G decreases. If this combination is used, the dose of the penicillin should be increased. When oral contraceptives are taken with tetracyclines, the effectiveness of the contraceptives decreases, and patients who take oral contraceptives should be advised to use an additional form of birth control while receiving the tetracycline.

Because oral tetracyclines are not absorbed effectively if taken with food or dairy products, they should be administered on an empty stomach 1 hour before or 2 to 3 hours after any meal or other medication.

The following nursing considerations should be taken into account as the nurses are providing care to patients receiving tetracyclines: Assess for possible contraindications or cautions. Perform a physical examination to establish baseline data for assessing the effectiveness of the drug and the occurrence of any adverse effects associated with drug therapy. Examine the skin for any rash or lesions to provide a baseline for possible adverse effects. Perform culture and sensitivity tests at the site of infection to ensure that this is the appropriate drug for this patient. Note respiratory status to provide a baseline for the occurrence of hypersensitivity reactions. Evaluate renal and liver function test reports, including blood urea nitrogen and creatinine clearance, to assess the status of renal and liver functioning, which helps to determine any needed changes in dose.

Tables 2.10 summarizing the prototype tetracyclines

	Tetracycline
Mechanism of action:	Inhibits protein synthesis in susceptible bacteria, preventing cell replication.
Indications:	Treatment of various infections caused by susceptible strains of bacteria; acne; when penicillin is contraindicated for eradication of susceptible organisms. The ophthalmic forms are indicated for bacterial conjunctivitis, trachoma (by preference use oral azithromycin for this indication), and prevention of neonatal conjunctivitis.
Contraindications	Hypersensitivity to the active substance, any of the tetracyclines or to any of its excipients; Chronic renal/ hepatic dysfunction; Renal impairment, Children under 8 years; Pregnancy and breastfeeding women. The ophthalmic preparation is contraindicated in patients who have fungal, mycobacterial, or viral ocular infections.
Adverse effects	Nausea, vomiting, diarrhea, glossitis, discoloring and inadequate calcifi cation of primary teeth of fetus when used in pregnant women or of secondary teeth when used in children, bone marrow suppression, photosensitivity, superinfections, rash, local irritation with topical forms.

Dosage and route:	Adult: 1–2 g/d PO in divided doses; Pediatric (>8 y): 25–50 mg/kg/d PO in four divided doses. The ophthalmic ointment is applied 2 times daily for 7 days (conjunctivitis) or 6 weeks (trachoma). One single application immediately after birth for prevention of neonatal conjunctivitis.
Dosage form:	Oral capsules and ophthalmic ointment.

	Doxycycline
Mechanism of action:	It acts by inhibiting bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria.
Indications:	Treatment of a wide variety of infections, including traveller's diarrhea and sexually transmitted diseases; periodontal disease and skin infections.
Contraindications	Contraindications of Doxycycline include: Liver disease due to rare fatal hepatotoxicity, History of yeast infections, Recent colitis caused by antibiotic use, kidney disease.
Adverse effects	The most common side effects of doxycycline are headaches, feeling or being sic, affecting growing teeth, thus it is not prescribed for children under 12 years old or given to pregnant and breastfeeding women. Do not drink alcohol while taking doxycycline.
Dosage and route:	Adult: 200 mg/day intravenous (IV) in two infusions of 1–4 hours each or 100–300 mg/day PO Pediatric (>8 year): 4.4 mg/kg/day PO.
Dosage form:	IV and oral forms exist.

Self-assessment 2.10

1) Which of the following antibiotics belongs to the class of tetracyclines?

   a) Doxycycline
   b) Erythromycin
   c) Amoxicillin
   d) Azithromycin

2) Why are tetracyclines contraindicated in children aged less than 8 years?

2.11 Class of sulphonamides (sulfonamides)

Learning Activity 2.11

1) Read the scenario below:

You receive a 52-year-old male patient who consults the health post where you are assigned in the clinical placement, with history of HIV infection. The patient says that he takes an antibiotic drug in addition to the antiretroviral drugs. He specifies that he was told that the antibiotic intends is to prevent the pneumonia caused by pneumocystis carinii. As a student nurse, you anticipate that the antibiotic may belong to the class of sulfonamides.

   a) List at least 2 antibiotics that belong to the class of sulfonamides
   b) What is the mechanism of action of sulfonamides?

CONTENT SUMMARY

The sulfonamides, or sulfa drugs, are drugs that inhibit folic acid synthesis. Sulfonamides include sulfadiazine, sulfasalazine, and cotrimoxazole (Bactrim).

Folic acid is necessary for the synthesis of purines and pyrimidines, which are precursors of RNA and DNA. For cells to grow and reproduce, they require folic acid. Humans cannot synthesize folic acid and depend on the folate in their diet to obtain this essential substance. Bacteria are impermeable to folic acid and must synthesize it inside the cell. The sulfonamides competitively block paraaminobenzoic acid to prevent the synthesis of folic acid in susceptible bacteria that synthesize their own folates for the production of RNA and DNA. This includes gram-negative and gram-positive bacteria such as Chlamydia trachomatis and Nocardia and some strains of H. influenzae, E. coli, and P. mirabilis.

Because of the emergence of resistant bacterial strains and the development of newer antibiotics, the sulfa drugs are no longer used much.

However, they remain an inexpensive and effective treatment for urinary tract infections (UTIs) and trachoma, especially in developing countries and when cost is an issue. These drugs are used to treat trachoma (a leading cause of blindness), nocardiosis (which causes pneumonias, as well as brain abscesses and inflammation), UTIs, and sexually transmitted diseases. Sulfasalazine is used in the treatment of ulcerative colitis and rheumatoid arthritis.

The sulfonamides are teratogenic; they are distributed into breast milk. These drugs, given orally, are absorbed from the Gastro-intestinal (GI) tract, metabolized in the liver, and excreted in the urine. The time to peak level and the half-life of the individual drug vary. Sulfadiazine is an oral agent slowly absorbed from the GI tract, reaching peak levels in 3 to 6 hours. Sulfasalazine is a sulfapyridine that is carried by aminosalicylic acids (aspirin), which release the aminosalicylic acid in the colon where is provides direct antiinflammatory effects. In a delayed-release form, this sulfa drug is also used to treat rheumatoid arthritis that does not respond to other treatments. It is rapidly absorbed from the GI tract, reaching peak levels in 2 to 6 hours. After being metabolized in the liver, it is excreted in the urine with a half-life of 5 to 10 hours. Cotrimoxazole is a combination drug that contains sulfamethoxazole and trimethoprim, another antibacterial drug. It is rapidly absorbed from the GI tract, reaching peak levels in 2 hours. After being metabolized in the liver, it is excreted in the urine with a half-life of 7 to 12 hours.

The sulfonamides are contraindicated with any known allergy to any sulfonamide, to sulfonylureas, or to thiazide diuretics because cross-sensitivities occur; during pregnancy because the drugs can cause birth defects, as well as kernicterus; and during lactation because of a risk of kernicterus, diarrhea, and rash in the infant. They should be used with caution in patients with renal disease or a history of kidney stones because of the possibility of increased toxic effects of the drugs.

Adverse effects associated with sulfonamides include GI effects such as nausea, vomiting, diarrhea, abdominal pain, anorexia, stomatitis, and hepatic injury, which are all related to direct irritation of the GI tract and the death of normal bacteria. Renal effects are related to the filtration of the drug in the glomerulus and include crystalluria, hematuria, and proteinuria, which can progress to a nephrotic syndrome and possible toxic nephrosis. CNS effects include headache, dizziness, vertigo, ataxia, convulsions, and depression (possibly related to drug effects on the nerves). Bone marrow depression may occur and is related to drug effects on the cells that turn over rapidly in the bone marrow. Dermatological effects include photosensitivity and rash related to direct effects on the dermal cells. A wide range of hypersensitivity reactions may also occur.

Nursing considerations: Assess for possible contraindications or cautions. Perform a physical assessment to establish baseline data for assessing the effectiveness of the drug and the occurrence of any adverse effects associated

with drug therapy. Examine skin and mucous membranes for any rash or lesions to provide a baseline for possible adverse effects. Obtain specimens for culture and sensitivity tests at the site of infection to ensure that this is the appropriate drug for this patient. Note respiratory status to provide a baseline for the occurrence of hypersensitivity reactions. Conduct assessment of orientation, affect, and reflexes to monitor for adverse drug effects and examination of the abdomen to monitor for adverse effects. Monitor renal function test findings, including blood urea nitrogen and creatinine clearance, to evaluate the status of renal functioning and to determine any needed alteration in dosage. Also perform a complete blood count (CBC) to establish a baseline to monitor for adverse effects.

Table 2.11 Summarizing the prototype sulfonamide

	Trimethoprim-Sulfamethoxazole (Cotrimoxazole/ BACTRIM ®)
Mechanism of action:	Trimethoprim, given together with sulfamethoxazole, produces sequential blocking in this metabolic sequence, resulting in marked enhancement of the activity of both drugs. Works by blocking two consecutive steps in protein and nucleic acid production, leading to inability for cells to multiply.
Indications:	Acute otitis media in children, Pneumocystis carinii pneumonia, shigellosis, systemic salmonella infections, urinary tract infections, and prostatitis. It is active against many respiratory tract pathogens; Pneumococcus, Haemophilus species, Moraxella catarrhalis, and Klebsiella pneumoniae.
Contraindications	Allergy to sulfonamides; glucose-6-phosphate dehydrogenase deficiency: Risk of hemolysis; due to immature hepatic enzymatic systems of the newborn, bactrim is contraindicated in: premature babies, newborn babies, the end of pregnancy and lactating mothers
Adverse effects	Nausea, vomiting, diarrhea, hepatocellular necrosis, hematuria, bone marrow suppression, Stevens–Johnson syndrome, rash, urticaria, photophobia, fever, chills
Dosage and route:	**Adults:** 2 tablets (of 480 mg each tablet) every 12 hours (two times a day). **Children:** 2 to 5 years (patients weighing less than 20 kg): 4 tablets of 120 mg in 2 divided doses; 6 to 12 years (patients weighing more than 20 kg): 8 tablets of 120 mg/day twice a day.
Dosage form:	Oral tablets and oral suspension

Self-assessment 2.11

1) Which of the following antibiotics belongs to the class of sulphonamides?
   a) Tetracycline
   b) Ciprofloxacin
   c) Streptomycin
   d) Cotrimoxazole
2) It is advisable to administer sulphonamides to pregnant women when indicated because they are safe during pregnancy. True or False

2.12 Medications used in treatment of bacterial sexually transmitted diseases

Learning Activity 2.12

Read carefully the scenario below and answer the questions related to it:

1) A 35-year-old-female patient finds you in the consultation room at the health post where you are placed in the clinical practice. She complains of lower abdominal pain and unusual whitish vaginal discharge that occurred two weeks after unprotected sexual intercourse. The patient is not pregnant and the physical assessment revealed that the patient has a tenderness of lower abdomen and the features of the urinary tract infection (UTI) have been excluded.
   a) In which category of syndromic management of STIs would you classify the symptoms of the client in the above scenario?
   b) Name the antibiotics that can be used in the syndromic management of this client?

CONTENT SUMMARY

Sexually transmitted infections are infections caused by bacteria, viruses and parasites that are transferred mainly via sexual contact, be it vaginal, anal, and oral or in some instances via non-sexual means, i.e. by means of blood or blood products. Mother-to-child transmission of for example chlamydia, gonorrhea, and syphilis occurs during pregnancy and childbirth. The most common causal agents are Chlamydia, Neisseria gonorrhoeae, treponema pallidum and trichomonas vaginalis.

Treatment of STIs relies on the syndromic approaches by taking note of observable clinical signs and symptoms patients complain of, and by making use of clinical algorithms or flow charts. Examples of observed syndromes include genital ulcers, abdominal pain, vaginal discharge and urethral discharge.

Vaginal discharge syndrome (VDS)

Vaginal discharge can be due to trichomoniasis, vaginosis (bacterial) and candidiasis but may also arise from N. gonorrhoeae and Chlamydia trachomatis infections.

Lower abdominal pain (LAP)

Pain in the lower abdominal region may be the result of pelvic inflammatory disease caused by N. gonorrhoeae and C. trachomatis infections.

Genital ulcer syndrome (GUS)

The presence of genital ulcers may be due to H. simplex, T. pallidum and H. ducreyi or a combination of these pathogens.

Male urethritis syndrome (MUS) and scrotal swelling (SSW)

N. gonorrhoeae or C. trachomatis or a combination of both may cause urethral discharge and scrotal swelling.

Table 2.12: COMMON SEXUAL TRANSMITTED DISEASES AND THEIR TREATMENT:

Sexual Transmitted Diseases (STDs)	Treatment
Gonococcal Urethritis	**First choice :** Ciprofloxacin, 500mg orally, BID for 7 days. (Contraindicated in pregnancy, children) or Azithromycin, 2g orally, or as a single dose Ceftriaxone, 250mg by intramuscular injection, as a single dose or Cefixime, 400mg orally, as a single dose or Spectinomycin, 4g (trobicin) by IM injection, or Doxycycline, 100mg orally, twice daily for 7 days. **If it is a complicated infection:** Ceftriaxone, 1g by IM or IV, once daily for 7 days or Spectinomycin, 2g by IM, twice daily for 7days.
Non gonococcal urethritis	Metronidazole, 2g orally, in a single dose or Tinidazole, 2g orally, in a single dose. **alternative regimen :** Metronidazole, 500mg orally, twice daily for 7 days or Tinidazole, 500mg orally, twice daily for 5 days.

Chlamydia Infections	Azithromycin 1 g orally as one dose or Doxycycline 200 mg orally daily for 10 days for patients allergic to macrolide (azithromycin) **For pregnant women:** Erythromycin 500mg 4 times per day for 7 days
Syphilis	**Early syphilis (primary, secondary):** **First choice recommended regimen:** Benzathine benzylpenicillin (Extecilline), 2.4 million IU, by intramuscular injection, at a single session per week for 3 weeks **Alternative regimen: Procaine benzyl penicillin, 1.2 million IU daily.** **Alternative regimen for penicillin-allergic non-pregnant patient:** Doxycycline, 100mg orally, twice daily for 15 days Or tetracycline, 500mg orally, 4 times daily for 15 days **Syphilis in pregnancy:** Erythromycin, 500mg orally, 4 times daily for 15 days or Erythromycin, 500mg orally, 4 times daily for 30 day if
Vaginal candidiasis	Metronidazole, 2g orally, in a single dose or Tinidazole, 2g orally, in a single dose **alternative regimen:** Metronidazole, 500mg orally, twice daily for 7 days or Tinidazole, 500mg orally, twice daily for 5 days Vaginal nystatin

NOTICE: All the time, the treatment guidelines and protocols are established by Rwanda Biomedical Canter and changed periodically.

Self-assessment 2.12

Read carefully the scenario below and answer the questions related to it:

1) Your colleague calls you for advice. He tells you that he receives a client in the consultation room presenting non painful ulcer on the opening of his penis, post unprotected sexual intercourse in the last 2 months. The physical examination reveals that the patient has no inguinal bubo. He also adds that it is the first time he meets with such case and he asks you the following questions:

   a) What is the diagnosis for this client based on the syndromic management of STIs?

   b) What antibiotic that can be used in this case based on the syndromic management of STIs?

2.13 Medications used in treatment of tuberculosis

Learning Activity 2.13

Read the case study below:

A 45-year-old female patient, weighing 65 kilos, is admitted to the health facility with cough, nocturnal hyperthermia, anorexia, asthenia, weight loss, and night sweating. She reports that these signs and symptoms have been there for the last 4 weeks.

She also reports having taken the full course of treatment with amoxicillin for 7 days that didn't help. The healthcare provider took a decision to take the sputum smear which became positive for Mycobacterium tuberculosis. The client is informed that she contracted pulmonary tuberculosis, and she is counselled that she will need to take all the antituberculosis drugs as prescribed. It is the first time for the patient to suffer from tuberculosis, and there is a need to immediately institute antituberculosis treatment.

   a) What are the names of antituberculosis drugs that must be used in the treatment of this patient?

   b) What are the treatment phases of tuberculosis?

CONTENT SUMMARY

Tuberculosis treatment refers to the medical treatment of tuberculosis (TB) which is an infectious disease that usually affects the lungs, but can affect other parts of the body.

As soon as diagnosis of tuberculosis is made, treatment must be initiated without delay and correct follow-up must be carried out in order to ensure the patient is completely cured. Inappropriate treatment can create drug resistance and increase the number of contagious cases in the community.

Basic principles for treatment

Treatment of tuberculosis has the following objectives:

- To cure tuberculosis patients, restore their quality of life and productivity
- Prevent death and long-term sequelae of TB
- Prevent relapses of TB
- Reduce the transmission of TB
- Prevent the development and transmission of resistance to anti-TB drugs.

Treatment of tuberculosis is based on a correct polychemotherapy:

- Including an appropriate and standardized association of at least four (4) drugs
- against tuberculosis, in order to avoid resistance
- Prescribed in adequate dosage for a sufficient duration
- Administered with supportive measures to patients, including information about the disease and its treatment, direct observation of treatment (DOT) and encouragement to complete treatment and achieve cure.

TREATMENT REGIMENS

A. First-line treatment

1. The most important drugs for the treatment of drug-susceptible TB are isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E).
2. Fixed-dose combinations (FDC) contain 2, 3 or 4 anti-tuberculosis drugs in the same tablet, which has the advantage of reducing the number of pills to be taken each day by the patient, reducing the risk of resistance and facilitating drug management.
3. Pediatric formulations are child-friendly medicines suitable for children weighing less than 25 kg. The tables do not need to be cut or crushed to obtain a suitable dose as they are dispersible in water in seconds and moreover, they have a pleasant taste. Each tablet should be put in a small amount of water (50 ml) to ensure that the child drinks all the quantity and takes the exact doses s/he needs. Children weighing 25 kg and above are treated with adult dosage and formulations.

Fixed-dose combinations for the treatment of drug-susceptible TB

Adults and children > 25 kg		
(RHZE)	(R_{150} mg + H_{75} mg + Z_{400} mg + E_{275} mg)	**Intensive phase**
(RH)	**(R_{150} mg + H_{75} mg)**	**Continuation phase**
Pediatric formulations (children < 25 kg)		
(RHZ)	**(R_{75}mg + H_{50} mg+ Z_{150}mg)**	Intensive phase
E	**Ethambutol 100mg**	Intensive phase
(RH)	**(R_{75} mg + H_{50} mg)**	Continuation phase

Rwanda uses the standard first-line regimen recommended by WHO for drug susceptible TB. It is a 6-month regimen including the intensive phase of 2 months with isoniazid, rifampicin, pyrazinamide and ethambutol followed by the continuation phase of 4 months with isoniazid and rifampicin. The medicines are taken once a day.

- This regimen is written $2(HRZE)_7$ /$4(HR)_7$, according to the international codification. The number preceding the letters indicates the duration of the phase in months and the backslash (/) separates the intensive phase from the continuation phase.
- A number after the parenthesis indicates the number of doses per week. No number or the number “7” indicates daily treatment.
- For patients who require TB retreatment (relapses, treatment after failure, treatment after interruption), the category II regimen (8 months) should no longer be prescribed.
- An XPert MTB/RIF test should be performed to guide the choice of treatment regimen

First-line regimen is indicated for:

- all bacteriologically confirmed cases, new and retreatments, which are susceptible to rifampicin (X pert result: MTB+/ RIF-).
- clinically diagnosed cases, pulmonary and extrapulmonary.

The standard first-line treatment is extended up to 12 months in case of tuberculous meningitis and osteoarticular TB. The intensive phase is unchanged (2 months) and the continuation phase is extended to 10 months (2RHZE/10RH).

The daily dosage is based on weight bands to facilitate medication management and administration to patients. Treatment should be started as soon as possible after bacteriological confirmation of the disease.

That is why any nurse previously trained in TB is authorized to prescribe and administer treatment for bacteriologically confirmed TB patients.

I. TREATMENT OF ADULTS and children ≥25 kg: 2 (RHZE) / 4 (RH)

Indicated for all new and previously treated cases who are susceptible to rifampicin and for clinically diagnosed, pulmonary and extrapulmonary TB.

Phase	Months / No doses	Drug	25-39 kg	40-54 kg	55 kg
Intensive	2 months (56 doses)	($R_{150}H_{75}Z_{400}E_{275}$)	2 Tab	3 Tab	4 Tab
Continuation	4 months (112 doses)	($R_{150}H_{75}$)	2 Tab	3 Tab	4 Tab

II. TREATMENT OF CHILDREN: 2 ($R_{75}H_{50}Z_{150}$) E_{100} / 4 (RH)

Indicated for all children weighing < 25 kg (new cases and previously treated).

Phase	Months / No doses	Drug	4-7 kg	8-11 kg	12-15 kg	16-24 kg	>25kg
Intensive	2 months (56 doses)	($R_{75}H_{50}Z_{150}$)	1 Tab	2 Tab	3 Tab	4 Tab	Use the adult dosage and tablets
		E_{100}	1 Tab	2 Tab	3 Tab	4 Tab	
Continuation	4 months (112 doses)	($R_{150}H_{75}$)	2 Tab	3 Tab	4 Tab		

Infant with weight below 4 kg: calculate the dose according to the table below.

DOSAGE		
Drug	**Children< 25 kg**	**Adults and children ≥25 kg**
Rifampicin (R)	15 mg/kg (10 to 20 mg/kg), max 600 mg/day	10 mg/kg (8 to 12 mg/kg), max 600 mg/day
INH (H)	10 mg/kg (7 to 15 mg/kg), max 300 mg/day	5 mg/kg (4 to 6 mg/kg), max 300 mg/day
Pyrazinamide (Z)	35 mg/kg (30 to 40 mg/kg)	25 mg/kg (20 to 30 mg/kg)
Ethambutol (E)	20 mg/kg (15 to 25 mg/kg)	15 mg/kg (15 to 20 mg/kg)

III.TB MENINGITIS AND OSTEOARTICULAR TB (new and retreatment): total duration 12 months:

- Adults and children 25 kg: 2 (RHZE) / $_{10}$ (RH)
- Children < 25 kg: 2 (RHZ)E / $_{10}$ (RH)

B. Second-line treatment regimen

MDR/RR-TB patients require a second-line treatment regimen. In line with WHO recommendations, Rwanda is introducing fully oral treatment regimens which are effective, less toxic and easier to take by patients then regimens containing injectables.

Second-line drugs used for DR-TB treatment in Rwanda

Group name	Anti-TB agent	Abbreviation
Fluoroquinolones	Levofloxacin moxifloxacin	Lfx Mfx
New drugs	bedaquilin delamanid	Bdq Dlm
Oral bacteriostatic second line anti-TB drugs	ethionamide prothionamide cycloserine p-aminosalicylic acid	Eto Pto Cs PAS
Other drugs	clofazimine linezolid	Cfz Lzd
Second-line injectable agents (aminoglycosides)	Kanamycin Amikacin capreomycin	Km Amk Cm

Standard second-line regimens include a short regimen and a long regimen.

Treatment regimens for DR-TB

INDICATION	REGIMEN	DURATION
Short treatment for: + newly diagnosed RR- and MDRTB	6 Bdq-4 Lfx-Pto-Cfz-Z-E $_{\text{-Hhigh-dose}}$/ 5 Mfx-Cfz-Z-E	9-11 months depending on the month of culture conversion
Long treatment regimen for: • previously treated MDR-TB • pre-XDR with resistance to aminoglycosides • XDR-TB	6 Bdq-Lzd-Lfx-Cfz or Cs/ 12 Lfx-Lzd-Cfz or Cs	18 months
Long treatment regimen for: • MDR-TB with resistance to FQ • XDR-TB	6 Bdq-Dlm-Lzd-Cfz-Cs / 12 Lzd-Cfz-Cs-Bdq or Dlm (depending on tolerance]	18 months

For details and dosage, see the RBC manual on “programmatic management of drug resistant tuberculosis”.

Pyridoxine (Vitamin B6) is used in the short treatment regimen and in the long regimen if cycloserine is used. Dosage: 25 to 50 mg/day.

Mono and polyresistance

Patients with isoniazid resistance and confirmed sensitivity to rifampicin should receive a treatment regimen with rifampicin, ethambutol, pyrazinamide and levofloxacin, with or without isoniazid, for a duration of 6 months: 6REZ-Lfx or 6(H) REZ-Lfx.

. Patients with poly-resistant tuberculosis, should receive an individualized regimen depending of the susceptibility profile.

Choice of TB treatment regimen

Reminder: all cases diagnosed with a positive sputum smear must have an Xpert MTB/RIF test. The choice of the appropriate regimen is based on the Xpert result, as follows**:**

- Patients susceptible to rifampicin (MTB+/RIF-), new and retreatment: treat with 2 RHZE/4RH.
- Patients with resistance to rifampicin (MTB+/RIF+):
  - If the bacillary load of the specimen tested is medium or high, refer the patient to a specialized MDR-TB center for 2d-line treatment. Send a specimen to the reference laboratory for LPA 1st and 2d line, culture and DST.
  - If the bacillary load is low or very low, repeat the Xpert test at the same laboratory with a fresh specimen and collect another specimen for culture and DST.
    - If rifampicin resistance is confirmed by the repeat test, refer the patient for 2dline treatment.
    - If rifampicin resistance is not confirmed by the repeat test, start first-line treatment and monitor with Xpert, culture and DST at month 1 and month 2. Reassess the regimen upon receipt of results.
- Patients with MTB+/RIF indeterminate: repeat the XPert test, start 2RHZE/4RH and send a good quality sputum sample to the reference laboratory for culture and DST.
- Re-evaluate the regimen upon receipt of results.
- Clinically diagnosed, pulmonary and extrapulmonary cases: give first-line regimen (2RHZE/4RH.)
- TB meningitis and osteoarticular TB: 2RHZE/10RH (total duration 12 months).

Administration of treatment

- Directly observed treatment (DOT) is recommended for all patients to ensure that they are taking treatment completely and to prevent the development of drug resistance.

- ✓ Each dose is given under the observation by a trained community health worker (CHW) or by a nurse at the health facility.
- ✓ The DOT provider gives the medication to the patient, observes the ingestion of the tablets and places a check mark on the treatment card. And this for all the doses, throughout the treatment.
- ✓ DOT administered by family members is not recommended. An exception is made for children because it can be difficult for them to receive their medicine from an unfamiliar DOT provider.
- ✓ For more details on DOT performed at community level, refer to the RBC community DOTS manual.

- First-line treatment
  - Patients are usually treated on an outpatient basis, which prevents the transmission of bacilli within health facilities.
  - All tablets should be taken together, preferably in the morning on an empty stomach. In case of nausea, heartburn or stomach pain, a light meal or porridge may be taken shortly before taking the medication.
  - Hospital admission may be clinically indicated:
    - ➢ When the patient's clinical condition is critical: acute forms (miliary), bedridden or severely malnourished patients, meningitis, abundant pleural effusion, severe hemoptysis, pneumothorax, etc.
    - ➢ In the event of severe drug toxicity.
    - ➢ When there are associated pathologies likely to influence the course of treatment: unbalanced diabetes, digestive ulcer, renal failure, heart failure, mental illness, AIDS during acute complication period, etc.
  - Smear-positive patients who need hospitalization must be separated from other patients, particularly from HIV-positive patients.

Second-line treatment

- In Rwanda, MDR-TB patients are admitted in a specialized MDR-TB centre to initiate second-line treatment.
- When they get two consecutive negative smears and one negative culture, they are referred to continue outpatient treatment at the health facility closest to their home.
- To facilitate administration of treatment under DOT, medication is given once a day whenever possible. Patients receive free holistic care, including treatment for drug-resistant TB, psychosocial and nutritional support, as well as outpatient transport costs.

- A standardized calendar of treatment monitoring is observed by all health facilities caring for DR-TB patients.
- For details, see the RBC manual on “programmatic management of drug-resistant tuberculosis”.

Promote treatment compliance

- The best way to guarantee success of treatment is regularity. Conversely, when the patient is irregular, the risk to develop resistance to antituberculosis drugs is high.
- A patient-centred approach should be used in order to promote treatment adherence, improve quality of life, and alleviate suffering. To this end, DOT should be delivered as close to the patient’s home as possible. The patient should be involved in the decision to take DOT at the health center or in the community and should receive counselling and encouragement several times during treatment (see chapter 8). In the event of the patient’s particular needs and to the extent possible, social support will be offered by mobilizing social assistance, government social programs, NGOs, churches, etc.
- Many patients quickly feel better after starting treatment and do not understand that they need to continue treatment. Emphasis should be placed on the importance of completing treatment and the consequences of incomplete treatment, such as the onset of drug resistance or more severe disease later.
- DOT enables the early identification of irregular patients and those lost to follow-up. Measures must be taken immediately for their recovery, such as appointing them to the health center, making a home visit to investigate the cause of the interruption and encourage continuation of treatment. In case of repeated irregularity or refusal to continue treatment, involve the family, or the chief of village or any other person having administrative or moral authority on the patient.
- As recuperation of patients lost to follow-up is sometimes laborious, it is always necessary to note on the patient’s card and in the TB register their full address, telephone number, the address of a family member, chief of village and nearest CHW.
- The attitude of caregivers towards patients contributes to compliance with treatment. A warm welcome, rapid administration of medicines with a few words of encouragement are crucial in making them feel confident and able to express any doubts or difficulties.

What to do in case of treatment interruption?

Patients who have stopped treatment for less than 8 consecutive weeks should restart or continue treatment, depending on the duration of the interruption and the phase of treatment during which the interruption occurs

Patients who have already taken at least 1 month of treatment and have interrupted for 8 consecutive weeks or more are declared “lost to follow-up”. These patients should have an XPert MTB/RIF test before resuming treatment in order to check susceptibility to rifampicin.

In some cases, such as prolonged interruption at the end of treatment or in a clinically diagnosed TB patient, the physician will decide whether to restart, continue or stop treatment, based on the clinic and additional examinations. These cases will be monitored clinically and new examinations will be performed in the event of resumption of symptoms. The result of treatment will be “lost to follow up”

Treatment of tuberculosis in particular situations

It is important to identify particular situations and comorbidities likely to influence the response to TB treatment and to manage them properly.

Pregnancy and breast-feeding

First-line antituberculosis drugs may be administered during pregnancy and are safe for the baby. Any pregnant woman who has been diagnosed with tuberculosis should be informed of the importance of taking anti-tuberculosis treatment for a successful pregnancy.

Second-line drugs have potential teratogenic effects, particularly injectable agents (kanamycin, amikacin) which may cause deafness to the baby and should be replaced by linezolid. The risks and benefits of treatment should be carefully evaluated by the physician and considered with the goal to protect the health of the mother and the child.

Contraception is strongly recommended for all non-pregnant women of childbearing age during the whole duration of second-line treatment. In case of bacteriologically confirmed tuberculosis during breast-feeding, the mother should immediately receive the adequate treatment regimen in order to prevent transmission of TB to the infant.

All first-line and second-line anti-tuberculosis drugs recommended for pregnant women may be administered to her. She will continue breast-feeding and if contagious, she should use a surgical mask until she becomes negative (smears and culture if MDR-TB). The baby will receive TB preventive treatment.

Contraceptive pill

Rifampicin may reduce the efficacy of the contraceptive pill. A higher dose pill should be prescribed (containing 50]g of estrogen) or another method of contraception may be used. Patients who vomit after taking an oral contraceptive can be at risk of decreased drug absorption and therefore of decreased TB treatment efficacy.

These patients should be advised to take their contraceptives apart from the anti-TB medicines and to use a barrier method until the contraceptive tablets are tolerated.

Diabetes mellitus

- Diabetes increases the risk of tuberculosis two- to three-fold. People with diabetes have worse tuberculosis treatment outcomes than people who do not have diabetes.
- Tuberculosis may impair glycemic control in people with diabetes.
- The 6-month standard regimen (2RHZE/4RH) is recommended for people with diabetes and drug-susceptible TB.
- Diabetes may potentiate the adverse effects of antiTB drugs, especially renal dysfunction and peripheral neuropathy.
- Pyridoxine should be provided for prevention of neuropathy (25 mg/day) or for its treatment (100 mg/day).
- Comprehensive treatment of diabetes includes counselling about increased physical activity, diet, and the administration of a glucose-lowering drug, metformin being the drug of choice.
- Diabetes must be managed closely throughout the TB treatment, in consultation with the diabetes expert.
- Infection control measures should be carefully implemented to reduce the risk of transmission of TB bacilli within the diabetes services
- Renal failure
- Avoid drugs which are eliminated by kidneys: ethambutol, and among second-line drugs: kanamycin, capreomycin and cycloserine.
- Alternative first-line regimen: 2RHZ / 4RH Great care should be taken in the administration of second-line drugs in patients with renal insufficiency.
- The dose and/or the interval between dosing should be adjusted for some second-line drugs when the creatinine clearance is 30 ml/min or for patients receiving hemodialysis.

Liver disorders

- Pyrazinamide, isoniazid and rifampicin are toxic for the liver. Pyrazinamide is the most hepatotoxic and rifampicin the least, although rifampicin is associated with cholestatic jaundice.
- Among the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs.

- Standard regimens may be used in case of previous history of viral hepatitis or in case of alcoholism, except in the event of severe chronic liver disease.
- These cases should be referred to a university hospital which will establish an alternative regimen.
- In the case of jaundice or hepatitis (transaminases above 3 times the normal value), stop antituberculosis drugs until jaundice disappears and transaminases decrease to less than 3 times the normal value; then reintroduce one anti-TB drug at a time with single tablets at progressive dose.

Malnutrition

- Patient's nutritional status should be assessed at the start of treatment. Patients with a body mass index (BMI) < 18.5 have an increased risk of death and relapse.
- These patients should be treated for malnutrition and tuberculosis.
- Administration of treatment in a health facility (HC or hospital) is desirable in order to ensure close clinical monitoring and adequate management of malnutrition.
- Nutritional support should be provided to patients with a BMI < 18.5 until they recover to a satisfactory nutritional state and to all patients under second-line treatment to foster treatment adherence.

Management of side effects

- The occurrence of adverse events during antituberculosis treatment can contribute to additional morbidity, treatment interruption or failure, emergence of drug resistance, reduced quality of life, and/or death.
- Close monitoring of patients is necessary so that side effects of anti-TB drugs are recognized quickly.
- One of the main advantages of directly observed therapy (DOT) over self-administration is the ability to monitor patients for side effects on a daily basis.
- Patients on anti-TB treatment should be informed about the possible adverse effects of the anti-TB medicines and the importance of reporting them.
- The majority of side effects are easy to recognize. The DOT provider must systematically check for their occurrence by using an appropriate checklist of symptoms (such as the one on the treatment card).

Self-assessment 2.13

1. What are the main objectives of tuberculosis treatment?
2. What is the standard first-line treatment regimen for drug-susceptible TB in Rwanda?
3. How should tuberculosis treatment be administered to ensure adherence and prevent drug resistance?
4. What adjustments should be made to tuberculosis treatment for pregnant women?
5. What is the recommended treatment for multidrug-resistant tuberculosis (MDR-TB) in Rwanda?

End of unit assessment 2

After going through the unit of antibiotics, attempt the following questions:

1) Which of the following terms refers to the ability of an antimicrobial drug to harm the target microbe without harming the host?
   a) Mode of action
   b) Therapeutic level
   c) Spectrum of activity
   d) Selective toxicity
2) Selective toxicity antimicrobials are easier to develop against bacteria because they are _____ cells, whereas human cells are eukaryotic
3) The spectrum of activity of an anti-infective indicates:
   a) The anti-infective's effectiveness against different invading organisms.
   b) The acidity of the environment in which they are most effective.
   c) The cell membrane type that the anti-infective affects.
   d) The resistance factor that bacteria have developed to this anti-infective.
4) A bacteriostatic substance is one that:
   a) Directly kills any bacteria it comes in contact with.
   b) Directly kills any bacteria that are sensitive to the substance.
   c) Drevents the growth of any bacteria.
   d) Prevents the growth of specific bacteria that are sensitive to the substance.

5) Ciprofloxacin, a widely used antibiotic, is an example of:

a) A penicillin

b) A fluoroquinolone.

c) An aminoglycoside.

d) A macrolide antibiotic

6) Which of the following is ototoxic and nephrotoxic?

a) Erythromycin

b) Doxycycline

c) Ampicillin

d) Gentamicin

7) Which of the following antibiotics is contraindicated in pregnant women and small children due to its tendency to irreversibly stain developing teeth?

a) Aminoglycosides

b) Tetracyclines

c) Penicillins

d) Fluoroquinolones

8) Which of the following is an example of an aminoglycoside antibiotic?

a) Azithromycin

b) Erythromycin

c) Streptomycin

d) Clindamycin

9) Differentiate a bacteriostatic antibiotic from bactericidal antibiotic.

10) Classify antibiotics into 5 categories according to their mechanism of action.

UNIT 3: ANTHELMINTIC (ANTIHELMINTHIC) DRUGS

Key Unit Competence

Utilize appropriate anti-helminthic drugs to manage different health conditions at the primary healthcare settings.

Introductory activity 3.0

1) What do you observe on the image above?
2) Have you ever seen the same scenario in your community? If yes, which drugs have you seen being used in the same scenario?

3.1. Introduction to anthelmintic drugs and deworming

Learning Activity 3.1

Read the scenario below:

A patient GN presents at your health clinic with the complaints of severe abdominal pain, vomiting and diarrhoea. For all physical examination performed, no signs of abnormalities found. All vital signs are normal and by history taking, his family lives in a region with poor sanitation. The laboratory results revealed the presence of eggs of ascaris during the direct stool examination. In addition, the patient tells you that he was given one year ago the drug as a single dose, the treatment which was given in mass campaign.

1) What is the disease do you think patient GN is suffering from?
2) Which of the following medications may be used in mass deworming?
   a) Tinidazole
   b) Mebendazole
   c) Metronidazole
   d) Amoxicillin
3) What are the classes of helminthic parasites that are often targeted in deworming?

CONTENT SUMMARY

Helminths are a broad range of organisms that include intestinal parasitic worms. There are three major groups of helminths namely: nematodes (roundworms), trematodes (flukes) and cestodes (tapeworms).

These groups of helminths are divided into two phyla; nematodes (roundworms) and platyhelminths (trematodes and cestodes). Infected people excrete helminth eggs in their faeces, which then contaminate the soil in areas with inadequate sanitation. Other people can then be infected by ingesting eggs or larvae in contaminated food, or through penetration of the skin by infective larvae in the soil (hookworms). Infestation can cause morbidity, and sometimes death, by compromising nutritional status, affecting cognitive processes, inducing tissue reactions, such as granuloma, and provoking intestinal obstruction or rectal prolapse. Control of helminthiasis is based on drug treatment, improved sanitation and health education. Over millions of preschool-age children and school-age children live in areas where these parasites are intensively transmitted, and are in need of treatment and preventive interventions.

Anthelminthics are a group of antiparasitic drugs that expel parasitic worms (helminths) and other internal parasites from the body by either stunning or killing them and without causing significant damage to the host. They may also be called vermifuges (those that stun) or vermicides (those that kill). Anthelmintics are used to treat people who are infected by helminths, a condition called helminthiasis. Pills containing anthelmintics are used in mass deworming campaigns of school-aged children in many developing countries. Anthelmintic are classified based upon their chemical structures.

i. **Piperazines:** eg. Diethylcarbamazine citrate, Piperazine citrate.
ii. **Benzimidazoles:** eg. Albendazole, Mebendazole, Thiabendazole.

Albendazole

Use: It is a new benzimidazole useful in the treatment of intestinal nematode infection and echinococcosis. It is effective against roundworm, hookworm, whipworm and threadworm infestations. It is effective in the treatment of ascariasis.

Mebendazole

Use: It is used in the treatment of hookworm, pinworm, and roundworm and whipworm infestation.

iii. Heterocyclics: eg. Oxamniquine, Praziquantel.

Praziquantel

Use: It is considered as drug of choice for the treatment of Schistosoma japonicum, (blood fluke) falciolopsiasis (intestinal flukes) clonorchiasis (chinese liver fluke) and opisthorchosis (liver fluke)

iv. Natural products: eg. Ivermectin, Avermectin.

Use: Ivermectin is widely used in veterinary practice for the control of endoparasite and exoparasite in domestic animals. It is also used to treat onchocerciasis in humans caused by round worm Onchocerca volvulus.

v. Vinyl pyrimidines : eg. Pyrantel, Oxantel.

Pyrantel

Use: The anthelmintic choice in the treatment of hookworm, pinworm and roundworm Infestations.

vi. Amide: eg. Niclosamide (Niclosan)

Use: The anthelmintic of first choice in the treatment of beef tapeworm, fish tapeworm, pork tapeworm and dwarf tapeworm infestations.

vii. Nitro derivative: eg. Niridazole.

viii. Imidazo thiazole: eg. Levamisole

Deworming is the giving of an anthelmintic drug to a human to rid them of helminths parasites, such as roundworm, flukes and tapeworm. Mass deworming campaigns of school children have been used both as a preventive as well as a treatment method for helminthiasis, which includes soil transmitted helminthiasis in children. Children can be treated by administering, for example, mebendazole and albendazole. According to the World Health Organization (WHO), over 870 million children (half of the children in the world) are at risk of parasitic worm infection.

Worm infections interfere with nutrient uptake, can lead to anemia, malnourishment and impaired mental and physical development, and pose a serious threat to children's health, education, and productivity. Infected children are often too sick or tired to concentrate at school, or to attend at all.

Self-assessment 3.1

1) Give the classes of anthelminthic drugs.
2) The deworming of children usually involves the use of mebendazole and coartem. True or False
3) Worm infections interfere with nutrient uptake, and can lead to anemia. True or False

3.2. Anthelmintic medications

Learning Activity 3.2

A patient X was admitted in a clinical health facility for intestinal worm infestation. After the laboratory investigations done, they found the eggs of hookworm in the stool. The healthcare providers decide to prescribe a drug that would be effective to manage the client's condition.

1) Which class of drugs can be used to manage the client's condition?
2) What is the mechanism of action of mebendazole?
3) What are the common side effects of albendazole?

CONTENT SUMMARY

Anthelmintic agents are indicated for the treatment of infections by certain susceptible worms and are very specific in the worms that they affect; they are not interchangeable for treating various worm infections. Treatment of a helminthic infection entails the use of an anthelmintic drug. Another important part of therapy for helminthic infections involves the prevention of reinfection or spread of an existing infection. Measures such as thorough hand washing after use of the toilet; frequent laundering of bed linens and underwear in very hot, chlorine-treated water; disinfection of toilets and bathroom areas after each use; and good personal hygiene to wash away ova are important to prevent the spread of the disease.

When the infestation is present or associated with complications occur, pharmacotherapy is initiated. Pharmacotherapy is targeted at killing the parasites locally in the intestine and systemically in the tissues and organs they have invaded.

Table Common anti-helminthic drugs

Drug	Route and adult dose (max dose where indicated)	Adverse effects
Albendazole (Albenza)	PO; 400 mg bid with meals (max: 800 mg/day)	Abnormal liver function tests, abdominal pain, nausea, vomiting Agranulocytosis, leukopenia
Ivermectin (Stromectol)	PO; 150–200 mcg/kg as a single dose	Fever, pruritus, dizziness, arthralgia, lymphadenopathy Acute allergic or inflammatory response
Mebendazole (Vermox)	PO; 100 mg as a single dose, or 100 mg bid for 3 days	Abdominal pain, diarrhea, rash Angioedema, convulsions
Praziquantel (Biltricide)	PO; 5 mg/kg as a single dose, or 25 mg/kg tid	Headache, dizziness, malaise, fever, abdominal pain cerebrospinal fluid (CSF) reaction syndrome
Pyrantel (Antiminth, Ascarel, Pin-X, Pinworm Caplets)	PO; 11 mg/kg as a single dose (max: 1 g)	Nausea, tenesmus, anorexia, diarrhea, fever No serious adverse effects

Mebendazole (Vermox)

Mechanism of action

Mebendazole is the most widely prescribed anthelmintic. Mebendazole is available in the form of a chewable tablet, and a typical 3-day course can be repeated in 3 weeks if needed. Mebendazole interferes with the ability to use glucose, leading to an inability to reproduce and cell death. It is used in the treatment of a wide range of helminth infections, including those caused by roundworm (Ascaris) and

pinworm (Enterobiasis). As a broadspectrum drug, it is particularly valuable in mixed helminth infections, which is more common in regions with poor sanitation. It is effective against both the adult and larval stages of these parasites. Because very little of mebendazole is absorbed systemically, it retains high concentrations in the intestine where it kills the pathogens. For pinworm infections, a single dose is usually sufficient; other infections require 3 consecutive days of therapy.

Pharmacokinetics

Very little of the mebendazole is absorbed systemically, so adverse effects are few. The drug is not metabolized in the body, and most of it is excreted unchanged in the feces. A small amount may be excreted in the urine.

Onset	Peak	Duration
2–4 h	1–7 h	3–9 h

Administration Alerts

- The drug is most effective when chewed and taken with a fatty meal.
- Pregnancy category C.

Adverse Effects: Because so little of the drug is absorbed, mebendazole does not generally cause serious systemic side effects. As the worms die, some abdominal pain, distention, and diarrhea may be experienced.

Contraindications: The only contraindication is hypersensitivity to the drug.

Interactions: Drug–Drug: Carbamazepine and phenytoin can increase the metabolism of mebendazole. Lab Tests: Unknown interaction with lab tests. Herbal/Food: High-fat foods may increase the absorption of the drug. Treatment of Overdose: There is no specific treatment for overdose.

Albendazole

Albendazole is an anthelmintic or anti-worm medication. It prevents newly hatched insect larvae (worms) from growing or multiplying in the body.

Mechanism of action

As a vermicide, albendazole causes degenerative alterations in the intestinal cells of the worm by binding to the colchicine-sensitive site of β-tubulin, thus inhibiting its polymerization or assembly into microtubules (it binds much better to the β-tubulin of parasites than that of mammals). Albendazole leads to impaired uptake of glucose by the larval and adult stages of the susceptible parasites, and depletes their glycogen stores. Albendazole also prevents the formation of spindle fibers needed for cell division, which in turn blocks egg production and development; existing eggs are prevented from hatching.

Pharmacokinetics

Oral absorption of albendazole varies among species, with 1–5% of the drug being successfully absorbed in humans, 20–30% in rats, and 50% in cattle.

The absorption also largely depends on gastric pH. People have varying gastric pHs on empty stomachs, and thus absorption from one person to another can vary wildly when taken without food. Generally, the absorption in the GI tract is poor due to albendazole's low solubility in water. It is, however, better absorbed than other benzimidazole carbamates. Food stimulates gastric acid secretion, lowering the pH and making albendazole more soluble and thus more easily absorbed.

Oral absorption is especially increased with a fatty meal, as albendazole dissolves better in lipids, allowing it to cross the lipid barrier created by the mucus surface of the GI tract. To target intestinal parasites, albendazole is taken on an empty stomach to stay within the gut. Absorption is also affected by how much of the albendazole is degraded within the small intestine by metabolic enzymes in the villi.

The pharmacokinetics of albendazole differ slightly between men and women: women have a lower oral clearance and volume of distribution, while men have a lower serum peak concentration

Common side effects

The most common side effects by albendazole are experienced by over 10% of people and include: Headache, neck stiffness, increased sensitivity to light, confusion; fever; nausea, vomiting, stomach pain; abnormal liver function tests; dizziness, spinning sensation; or temporary hair loss.

Ivermectin (Stromectol)

Stromectol is a prescription medicine used to treat the symptoms of certain parasite infections (Strongyloidiasis of the Intestinal Tract and River Blindness/ Onchocerciasis). Stromectol may be used alone or with other medications.

Mechanism of action

Ivermectin is an anti-parasitic medication. Ivermectin works by binding to invertebrate muscle and nerve cells of parasites, causing paralysis and death of parasites. Ivermectin is active against the non-adult form of Onchocerca volvulus.

Pharmacokinetics

Ivermectin is readily absorbed from the GI tract and reaches peak plasma levels in 4 hours. It is completely metabolized in the liver with a half-life of 16 hours; excretion is through the feces.

Indications

STROMECTOL (ivermectin) is indicated for the treatment of the following infections: Strongyloidiasis of the intestinal tract. Stromectol (ivermectin) is indicated for the treatment of intestinal (i.e., nondisseminated) strongyloidiasis due to the nematode parasite Strongyloides stercoralis. Is indicated for the treatment of onchocerciasis due to the nematode parasite Onchocerca volvulus.

Doses

The recommended dosage of Stromectol for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 mcg of ivermectin per kg of body weight. Patients should take tablets on an empty stomach with water.

Side effects

The most common side effects of Stromectol include: Headache, muscle aches, dizziness, nausea, diarrhea, and mild skin rash

Contraindications / Precautions

It contraindicated in asthma, hepatic disease, human immunodeficiency virus (HIV) infection, immunosuppression, pregnancy, breast-feeding, children, infants.

Praziquantel

Praziquantel is used to treat infections caused by Schistosoma worms

Mechanism of action

The action of praziquantel is limited very specifically to trematodes and cestodes; nematodes (including filariae) are not affected. Praziquantel works by causing severe spasms and paralysis of the worms' muscles. This paralysis is accompanied - and probably caused - by a rapid Ca 2+ influx inside the schistosome

Pharmacokinetics

The absorption of praziquantel is rapid and nearly complete but the systemic bioavailability of praziquantel is low and varies considerably between individuals. After the administration of 40 mg/kg to fasted healthy adults Oral drugs have a greater pharmacokinetic variability than drugs administered by the intravenous route, explained by the blood flow at the absorption site, the absorptive surface area, the transit time and the gastric pH, factors all influenced by concurrent food uptake

Dosages of Praziquantel:

Adult and pediatric drug dosages:

Dosage considerations should be given as follows:

Adult drug dosage: 20 mg/kg orally three times per day for 1 day, every 4-6 hours

Pediatric drug dosage: Children under 4 years old: safety and efficacy not established

Children 4 years and older: 20 mg/kg orally three times daily for 1 day, every 4-6 hours

Contraindication

BILTRICIDE (praziquantel) is contraindicated in patients who previously have shown hypersensitivity to the drug or any of the excipients. Since parasite destruction within the eye may cause irreversible lesions, ocular cysticercosis must not be treated with this compound.

Side effects

Abdominal pain, allergic reaction, cerebrospinal reaction syndrome, diarrhea, dizziness, drowsiness, feeling unwell (malaise), fever, headache, hives, itching, mild fever, mild skin rash, nausea, rash, sweating, tired feeling, upset stomach, vomiting.

Self-assessment 3.2

1) Which of the following drugs can be used in the treatment of schistosoma infection?

   a) Praziquantel

   b) Ivermectin

   c) Albendazole

   d) Mebendazole

2) What is the mechanism of action of albendazole?

3) As a nurse student in the clinical placement, you are providing health education to a patient who is taking albendazole. Which of the following statements should be included in your teaching?

   a) Oral absorption is especially decreased with a fatty meal, and it should not never be taken with fatty meal

   b) Albendazole dissolves better in water, and drinking a lot of water speeds up its absorption

   c) Albendazole can never cross the lipid barrier created by the mucus surface of the GI tract.

   d) To target intestinal parasites, albendazole is taken on an empty stomach to stay within the gut.

3.3. National Guidelines for Deworming and WHO Community Deworming

Learning Activity 3.3

1) Which activity does the image above indicate?
2) Which medications and at which doses does the WHO recommend for deworming using annual or biannual single-dose as a public health intervention for children aged 7 years old?
3) Deworming of children and pregnant women and children through the health services and in schools is well established and can help to reduce iron deficiency. True or False

CONTENT SUMMARY

Those living in poverty are most vulnerable to infection which can impair nutritional status by causing internal bleeding which can lead to loss of iron and anemia; intestinal inflammation and obstruction; diarrhea; and impairment of nutrient intake, digestion and absorption.

Evidence shows that preventive chemotherapy, or the periodic large-scale administration of anthelminthic medicines to populations at risk, can dramatically reduce the burden of worms caused by soil-transmitted helminth infections.

Preventive chemotherapy is an important part of a comprehensive package to eliminate morbidity due to soil-transmitted helminths in at-risk populations. However, long-term solutions to soil-transmitted helminth infections will need to address many factors, including improvements in water, sanitation and hygiene.

The WHO recommends Preventive chemotherapy (deworming), using annual or biannual single-dose albendazole (400 mg) or mebendazole (500 mg) as a public health intervention for all young children 12–23 months of age, preschool children 1–4 years of age, and school-age children 5–12 years of age living in areas where

the baseline prevalence of any soil-transmitted infection is 20% or more among children, in order to reduce the worm burden of soil-transmitted helminth infection.]

Self-assessment 3.3

1) What is the important part of a comprehensive package to eliminate morbidity due to soil-transmitted helminths in at-risk populations?
2) Discuss on how deworming is being applied in your community?

End of unit assessment 3

1) What are the three major groups of helminths?
2) Which of the following can be classified in heterocyclics ?
   a) Piperazine citrate.
   b) Thiabendazole
   c) Mebendazole
   d) Praziquantel
3) Ivermectin is classified among natural products category of anthelminthic drugs. True or False.
4) Which of the following are the most commonly used medications in deworming?
   a) Mebendazole and albendazole
   b) Mebendazole and tinidazole
   c) Mebendazole and Ivermictin
   d) Ivermictin and albendazole
5) Due to its effectiveness, praziquantel is the drug of choice for filariae. True or False
6) The deworming is the giving of an anthelmintic drugs human to help them get rid of:
   a) Roundworms, flukes and protozoa
   b) Roundworms, flukes and tapeworm
   c) Flukes, protozoa and tapeworm
   d) Protozoa, tapeworm and roundworms

UNIT 4: ANTIPROTOZOAL DRUGS

KEY UNIT COMPETENCE

Utilize antiprotozoal drugs to manage different health condition at the primary healthcare settings

Introductory activity 4.0

1) The images above show two different medications used in management of protozoal diseases.
   a) Have you ever seen or used any of the medications above?
   b) Which conditions does the above medications are indicated?

4.1. Definition and Classification of antiprotozoal medications

Learning Activity 4.1

Read the scenario below carefully and try to find answers to the following questions:

A client X was received at health post complaining of fever, chills and arthralgia for 3 days and diarrhea for 2 days. The laboratory results reveal positive blood smear and Entamoeba histolytica in the stool.

a) Read the book of pharmacology in the library, and define antiprotozoal medication and list the classes of antiprotozoal drugs.

b) Think about the drugs you can give to the patient X in the scenario

CONTENT SUMMARY

Protozoans are single-celled organisms that are the smallest and simplest members of the animal kingdom. This topic will focus on the chemotherapy to treat diseases caused by Trypanosoma cruzi (Chagas' disease), Trypanosoma b. gambiense and Trypanosoma b. rhodesiense (sleeping sickness), Plasmodium (malaria), Leishmania (leishmaniasis) and amebiasis.

Protozoal diseases are less easily treated than bacterial infections because many of antiprotozoal drugs cause serious toxic effects and most of them are not safe in pregnancy and unicellular protozoal cells have metabolic processes closer to human cells than bacteria.

Antiprotozoal drug is a drug that destroys protozoans, inhibits their growth, ability to reproduce and prevent the development of protozoans in humans. The actions of antiprotozoal drugs against the infections are complex and are not fully understood. Some of them may interfere with reproduction of or damage protozoal DNA to limit the spread of an infection. Antiprotozoal drugs are classified into 2 classes: antimalarial drugs and miscellaneous antiprotozoals.

Antimalarial drugs

Antimalarial drugs include mefloquine, chloroquine, proguanil with atovaquone and doxycycline. They kill or inhibit the growth of protozoa by affecting different stage of the parasitic life cycle. They are used both to treat and prevent malaria.

Miscellaneous antiprotozoals

Commonly used miscellaneous antiprotozoals include metronidazole, tinidazole and so on. Metronidazole is the most common treatment for trichomoniasis and giardiasis. Its action in the treatment of protozoal infections remains poorly understood, however, it may work by damaging protozoal DNA. Tinidazole works as well as metronidazole and has many of the same side effects, but it can be given in a single dose. See table 3.1.1 below:

The table 4.1: The classifications of antiprotozoal (Drugs of choice for protozoal infection), causative protozoa, and disease

Antiprotozoal drugs		
Disease	**Causative Protozoan**	**Drugs of Choice**
Malaria	Plasmodium	Quinine, artésunate and coartem
Amebiasis	Entamoeba histolytica	metronidazole, tinidazole
Giardiasis	Giardia lamblia	Metronidazole, tinidazole, nitazoxanide

Leishmaniasis	Leishmania species	Sodium stibogluconate, amphotericin B, miltefosine
Toxoplasmosis	Toxoplasma gondii	Pyrimethamine plus sulfadiazine
Trichomoniasis	Trichomonas vaginalis	Metronidazole, tinidazole
Trypanosomiasis	Trypanosoma	Metronidazole tinidazole
American (Chagas' disease)	Trypanosoma cruzi	Nifurtimox, benzimidazole
East African (sleeping sickness)	Trypanosoma brucei rhodesiense	

Self-assessment 4.1

The medical clinic has received 3 patients this morning. Patient A is being seen for an intestinal disorder that he acquired after swimming in a local lake and be diagnosed for giardiasis. Patient B has acquired immunodeficiency syndrome (AIDS) and is showing early signs of pneumonia. After clinical review he/she was diagnosed for pneumocytosis. Patient C is being treated and evaluated on a regular basis for a sexually transmitted infection and was diagnosed with trichomoniasis.

1) Select the drugs you feel the physician is likely to prescribe for patient A
   a) Chloroquine,
   b) Artemisinin,
   c) Amoxicillin
   d) Metronidazole
2) Select the drugs you feel the physician is likely to prescribe for patient B
   a) Chloroquine,
   b) Artemisinin,
   c) Pentamidine
   d) Nitazoxanide
3) Select the drugs you feel the physician is likely to prescribe for patient C
   a) Artemisinin,
   b) Metronidazole
   c) Chloroquine
   d) Suramin

4.2. Plasmodium's life cycle

Learning Activity 4.2

1) Read the scenario below and answer related questions: A 40 years old female is brought to you with a history of fever for 2 days, chills, headache, and arthralgia. On examination, you find that she weighs 63 kg, has temperature of 39.2 ^{0}C. A blood slide reveals plasmodium falciparum ring stage ++
   a) According to you, what should be the diagnosis for this case?
   b) What are two main phases of the disease development?
   c) How is the disease transmitted?
   d) Is the disease preventable?
2) Which of the following is infective form of plasmodium for human?
   a) Schizont
   b) Merozoite
   c) Sporozoites
   d) Oocyst

Content summary

Malaria is a disease characterized by a cycle of fever and chills transmitted through a bite of a female Anopheles mosquito. Identified causes include Plasmodium falciparum, vivax, malariae, and ovale. Malaria is endemic in many parts of the world.

Sporozoites travel through bloodstream and become lodged in the liver and other tissues.

In approaching the antimalarial drugs, we begin by reviewing the life cycle of the malaria parasite in order to understand the drugs, specific applications of antimalarial drugs and the rationale behind treatment of patients with malaria.

Malaria develops via two phases: an exoerythrocytic and an erythrocytic phase. The exoerythrocytic phase involves infection of the hepatic system, or liver, whereas the erythrocytic phase involves infection of the erythrocytes, or red blood cells. When an infected mosquito pierces a person's skin to take a blood meal, sporozoites in the mosquito's saliva enter the bloodstream and migrate to the liver. Within minutes of being introduced into the human host, the sporozoites infect hepatocytes, multiplying asexually and asymptomatically for a period of over 5-16 days depending on the species. Once in the liver, these organisms differentiate to

yield thousands of merozoites, which, following rupture of their host cells, escape into the blood and infect red blood cells, thus beginning the erythrocytic stage of the life cycle.

Then, the merozoites infect red blood cells, where they develop into ring forms, trophozoites and schizonts which in turn produce further merozoites over 1-3 days depending on the species.

This asexual multiplication can result in thousands of parasite-infected cells in the host bloodstream, leading to illness and complications of malaria that can last for months if not treated. Some of the merozoite-infected blood cells leave the cycle of asexual multiplication.

Instead of replicating, the merozoites in these cells develop into sexual forms of the parasite, called male and female gametocytes, that circulate in the bloodstream which, if taken up by a mosquito, will infect the insect and continue the life cycle. When a mosquito bites an infected human, it ingests the gametocytes.

In the mosquito gut, the infected human blood cells burst, releasing the gametocytes, which develop further into mature sex cells called gametes. Male and female gametes fuse to form diploid zygotes, which develop into actively moving ookinetes that burrow into the mosquito midgut wall and form oocysts. Growth and division of each oocyst produces thousands of active haploid forms called sporozoites. After 8-15 days, the oocyst bursts, releasing sporozoites into the body cavity of the mosquito, from which they travel to and invade the mosquito salivary glands. The cycle of human infection restarts when the mosquito takes a blood meal, injecting the sporozoites from its salivary glands into the human bloodstream.

Some P. vivax and P. ovale sporozoites do not immediately develop into exoerythrocytic phase (merozoites), but instead produce hypnozoites that remain dormant for periods ranging from several months (6–12 months typically) to as long as three years. After a period of dormancy, they reactivate and produce merozoites. Hypnozoites are responsible for long incubation and late relapses in these two species of malaria.

The fever in malaria occurs at the end of erythrocytic phase. During this phase, the merozoites lyse the Red blood cell (RBCs) and this hemolysis is accompanied by the release of hemozoin pigment which directly goes and disturbs the hypothalamic functioning and causes the occurrence of fever.

The erythrocytic phase occurs every 48 hours in cases of P. falciparum, P. vivax and P. ovale and 72 hours in case of P. malariae. Thus, P. falciparum causes the malignant form of tertian fever, P. vivax and P. ovale are responsible for the benign form of Tertian fever (fever occurring at every 3rd day or after 2 days) and P. malariae is responsible for quartan fever (fever occurring at every 4th day or after 3 days). Then, the fever is intermittent (fever occurring at regular intervals).

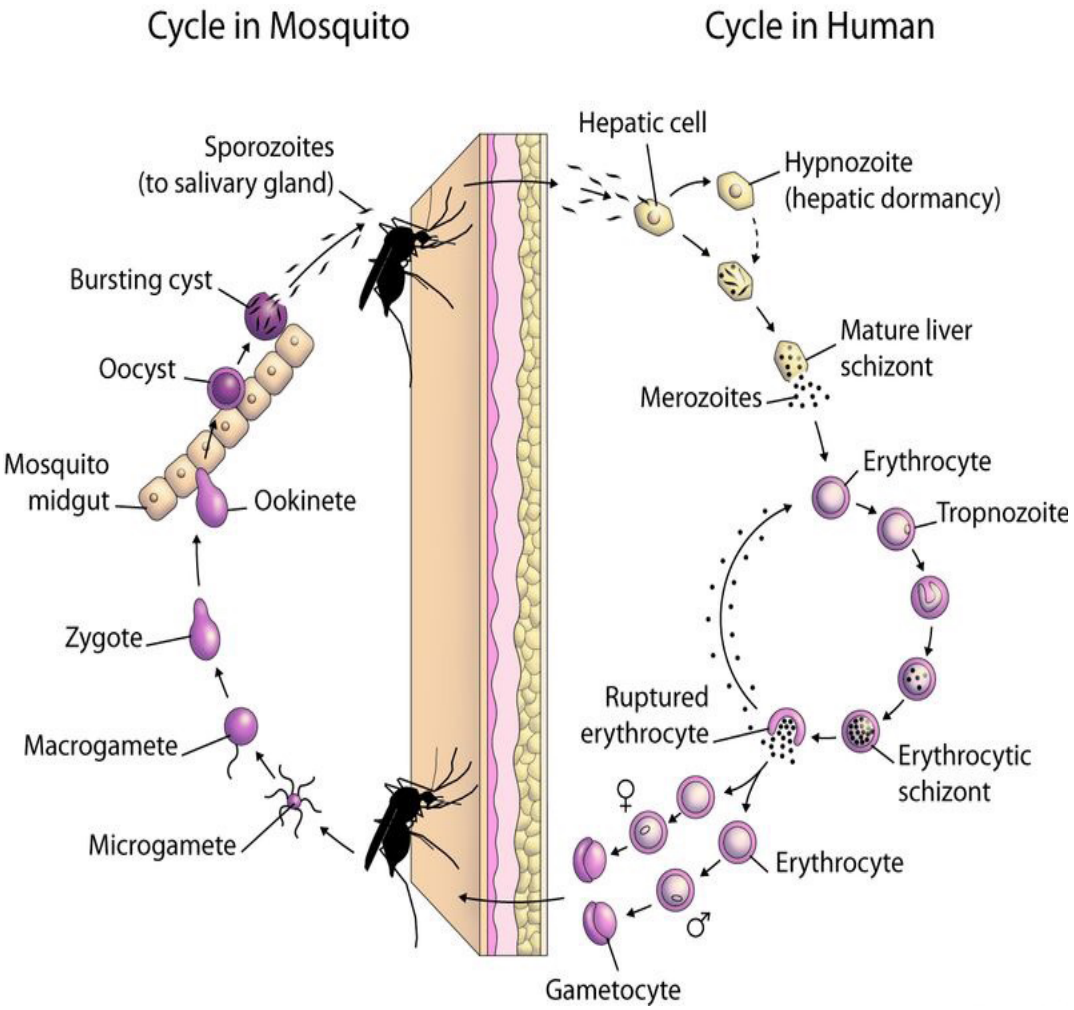


Figure: Plasmodium's life cycle

Self-assessment 4.2

1) Fever during malaria disease is associated with which of the following phenomena in malaria cycle?

   a) The exoerythrocytic phase involves infection of the hepatic system, or liver and gives rise fever

   b) When an infected mosquito pierces a person's skin to take a blood meal, sporozoites infect the liver then fever developed.

   c) During the phase of erythrocytic, the merozoites lyse the Red blood cells (RBCs) and this hemolysis is accompanied by the release of hemozoin pigment which directly goes and disturbs the hypothalamic functioning and causes the occurrence of fever.

   d) Instead of replicating, the merozoites develop into sexual forms of the parasite, called male and female gametocytes, that circulate in the bloodstream and disturbs the hypothalamic function that cause fever.

2) Using library book and internet, state the body areas/parts affected in the following phases of malaria development:

   a) Exoerythrocytic phase

   b) Erythrocytic phase

3) Which of the following species of plasmodium causes quartan fever?

   a) Plasmodium vivax

   b) Plasmodium ovale

   c) Plasmodium malariae

   d) Plasmodium falciparum

4) Which of the following species of plasmodium causes malignant form of tertian fever?

   a) Plasmodium vivax

   b) Plasmodium ovale

   c) Plasmodium malariae

   d) Plasmodium falciparum

5) Which of the following species of plasmodium causes benign form of tertian fever?

   a) Plasmodium vivax

   b) Plasmodium ovale

   c) Plasmodium malariae

   d) a and b

4.3. Antimalarial medications

Learning Activity 4.3

1) The nurse is reviewing the medication history of a patient who is taking Coartem. However, the patient's chart reveals a history of fever, headache and polyarthralgia. The patient is most likely taking this medication for:

   a) Plasmodium.

   b) Thyroid disorders.

   c) Roundworms.

   d) Rheumatoid arthritis.

2) Identify three antimalarial medications used in Rwanda that you know.

3) What malaria prophylaxis approach will you recommend for travellers visiting malaria endemic area?

CONTENT SUMMARY

Our goal in this sub-lesson is to describe the Antimalarial medications. One of the greatest protozoal problems worldwide is the treatment and prevention of malaria.

Antimalarials are agents used to attack Plasmodium at various stages of its life cycle. Through this, it becomes possible to prevent acute malarial reaction in individuals who have been infected by the parasite.

Antimalarial drugs can be classified according to antimalarial activity and according to structure.

1. According to antimalarial activity:

Tissue schizonticides for causal prophylaxis: These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented. Pyrimethamine and Primaquine have this activity. However, since it is impossible to predict the infections before clinical symptoms begin, this mode of therapy is more theoretical than practical.

Tissue schizonticides for preventing relapse: These drugs act on the hypnozoites of P. vivax and P. ovale in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.

Blood schizonticides: These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in antimalarial chemotherapy. These include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, Tetracyclines etc.

Gametocytocides: These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against P. vivax and P. malariae, but not against P. falciparum. Primaquine has gametocytocidal activity against all plasmodia, including P. falciparum.

Sporontocides: These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

Thus in effect, treatment of malaria would include a blood schizonticide, a gametocytocide and a tissue schizonticide (in case of *P. vivax* and *P. ovale*). A combination of chloroquine and primaquine is thus needed in ALL cases of malaria.

Principles of antimalarial therapy are based on therapeutic objectives. Drug responsiveness of the malaria parasite changes as the parasite goes through its life cycle. The erythrocytic forms are killed with relative ease, whereas the exoerythrocytic (hepatic) forms are much harder to kill and sporozoites do not respond to drugs at all. Because sporozoites are insensitive to available drugs, drugs cannot prevent primary infection of the liver.

Because of these differences, antimalarial therapy has three separate objectives/ Three methods used to eradicate malaria: (1) treatment of an acute attack (clinical cure), (2) prevention of relapse (radical cure), and (3) prophylaxis (suppressive therapy).

- **Treatment of an acute attack**

Clinical cure is accomplished with drugs that are active against erythrocytic forms of the malaria parasite. By eliminating parasites from red blood cells, the erythrocytic cycle is stopped and symptoms cease.

For patients with vivax malaria, clinical cure will not prevent relapse, because hypnozoites remain in the liver. However, for patients with falciparum malaria, successful treatment of the acute attack prevents further episodes.

For mild to moderate malaria, oral therapy is employed. Chloroquine is the drug of choice for an acute attack caused by chloroquine-sensitive strains of P. falciparum or P. vivax. As a rule, a 3-day course of treatment produces clinical cure. For strains of P. falciparum or P. vivax that is chloroquine resistant, quinine is a drug of first choice, combined with either doxycycline, tetracycline, or clindamycin.

Malarone, a fixed-dose combination of atovaquone plus proguanil, is an effective alternative. Mefloquine may also be used but is considered less desirable owing to concerns about neuropsychiatric effects.

For severe malaria caused by P. falciparum or P. vivax, parenteral therapy is required. Quinidine gluconate is approved by the Food and Drug Administration

(FDA) for parenteral use in malaria. When used for severe malaria, IV quinidine should be combined with doxycycline, tetracycline, or clindamycin. An alternative to quinidine, known as artesunate, is recommended by the World Health Organization.

The various antimalarial drugs work during different phases of the parasite's growth inside the human. The antimalarials that exert the greatest effect on all four Plasmodium organisms during the erythrocytic or blood phase are chloroquine, hydroxychloroquine, and pyrimethamine.

Primary tissue schizonticides (eg, primaquine) kill schizonts in the liver, whereas blood schizonticides (eg, chloroquine, quinine) kill these parasitic forms only in the erythrocyte.

Sporonticides (proguanil, pyrimethamine) prevent sporogony and multiplication in the mosquito. Other drugs that are known to work during the blood phase are quinine, quinidine, and mefloquine.

The most effective antimalarial drug for eradicating the parasite during the exoerythrocytic phase is primaquine, which works during both phases. Primaquine is indicated specifically for infection with P. vivax.

Chloroquine and hydroxychloroquine (4-aminoquinolines) are the drugs of choice for the treatment of susceptible strains of malarial parasites. They are highly toxic to all Plasmodium spp., except resistant strains of P. falciparum. Pyrimethamine is an antimalarial antibiotic that is used in combination with the sulfonamide antibiotic sulfadoxine (Fansidar) for prophylaxis against chloroquine-resistant P. falciparum and P. vivax.

The drug combination atovaquone and proguanil (Malarone) is also used for prevention and treatment of P. falciparum infection.

Antimalarial drugs administered to humans cannot affect the parasite during its sexual cycle when it resides in the mosquito. Instead, these drugs work against the parasite during its asexual cycle, which takes place within the human body. Often these drugs are given in various combinations to achieve an additive or synergistic antimalarial effect. One example is the combination of the two antiprotozoal drugs atovaquone and proguanil (Malarone). The antibiotic combination of pyrimethamine and sulfadoxine (Fansidar) is also commonly used, especially in cases caused by drug-resistant organisms.

The mechanisms of action of the various antimalarial drugs differ depending on the chemical family to which they belong.

The drug effects of the antimalarial drugs are mostly limited to their ability to kill parasitic organisms, most of which are Plasmodium species (spp.). However, some of these drugs have other effects and therapeutic uses.

Hydroxychloroquine also has anti-inflammatory effects and is sometimes used in the treatment of rheumatoid arthritis and systemic lupus erythematosus. Quinine and quinidine can also decrease the excitability of both cardiac and skeletal muscles. Quinidine is still used to treat certain types of cardiac dysrhythmias.

- **Prevention of relapse**

People infected with P. vivax harbor dormant parasites in the liver, in order to prevent relapse, a drug that can kill these hepatic forms must be taken. The use of drugs to eradicate hepatic P. vivax is referred to as radical cure. The agent of choice for preventing relapse of vivax malaria is primaquine, a drug that is highly active against the hepatic forms of P. vivax. For falciparum malaria, no treatment is needed, since relapse does not occur following clinical cure.

P falciparum and P malariae have only 1 cycle of liver cell invasion. The other species have a dormant hepatic stage responsible for recurrent infections and relapses.

- **Prophylaxis**

Selection of drugs for prophylaxis is based on the drug sensitivity of the plasmodial species found in the region to which travel is intended.

Malaria can often be avoided by using the ABCD approach which are both drugs and nondrug prevention measures (Awareness of risk, bite prevention, check whether you need to take malaria prevention tablets and diagnosis).

a) Awareness of risk: find out whether the patient is at risk of getting malaria. It's important to visit a health care provider before the travel for advice, check whether it is necessary or need to take preventative malaria treatment depending on the country you are visiting. Some country it is not necessary to take preventative malaria treatment before travelling. Even if you grew up in a country where malaria is common, you still need to take precautions to protect yourself from infection if you're travelling to a risk area.

NB: In area where malaria vaccine is not yet introduced, health care provider has to educate people that nobody has complete immunity to malaria, and any level of natural protection you may have had is quickly lost when you move out of a risk area.

There's vaccine available currently approved by world health organization that offers protection against malaria. A first Malaria Vaccine Approved by W.H.O. RTS, S/ASO1 (RTS. S), trade name Mosquirix, which was endorsed by the World Health Organisation (WHO) on Wednesday (October 6/2021), is the first and, to date only, vaccine shown to have the capability of significantly reducing malaria, and life-threatening severe malaria, in tests on young African children and it requires four injections.

The RTS, S/AS01 (RTS, S) malaria vaccine is one of two safe and effective vaccines recommended by WHO to prevent malaria in children. If implemented widely, malaria vaccines could save tens of thousands of lives each year. The vaccine's use requires at least three doses in infants by age 2, with a fourth dose extending the protection for another 1–2 years.

b) Bite prevention: avoid mosquito bites by using insect repellent, covering your arms and legs, and using a mosquito net. It's not possible to avoid mosquito bites completely, but the less you're bitten, the less likely you are to get malaria.

c) Check whether you need to take malaria prevention tablets: if you do, make sure you take the right antimalarial tablets at the right dose, and finish the course to reduce the chances of getting the disease until vaccine become available for all.

However, antimalarials only reduce the risk of infection by about 90%, so taking steps to avoid bites is also important.

Depending on the type you're taking, continue to take the tablets for up to 4 weeks after returning from the trip to cover the incubation period of the disease.

NB: In some cases, you may be prescribed emergency standby treatment for malaria before you travel. This is usually if there's a risk of you becoming infected with malaria while travelling in a remote area with little or no access to medical care.

Examples of emergency standby medications include:

Atovaquone with Proguanil

Artemether with Lumefantrine

Quinine plus Doxycycline

Quinine plus Clindamycine

The list below outlines which medications are safe or unsafe to use while pregnant:

Mefloquine: not usually prescribed during the first trimester of pregnancy, or if pregnancy is a possibility during the first 3 months after preventative antimalarial medication is stopped. This is a precaution, even though there's no evidence to suggest mefloquine is harmful to an unborn baby.

Doxycycline: never recommended for pregnant or breastfeeding women as it could harm the baby.

Atovaquone plus proguanil: not generally recommended during pregnancy or breastfeeding because research into the effects is limited. However, if the risk of malaria is high, they may be recommended if there's no suitable alternative.

Chloroquine combined with proguanil is suitable during pregnancy, but it is rarely used as it's not very effective against the most common and dangerous type of malaria parasite.

d) Diagnosis: Malaria can get worse very quickly, so it's important that it's diagnosed and treated as soon as possible.

Treatment for malaria is not initiated until the diagnosis has been confirmed by laboratory tests and it is recommended that the treatment should be completed once the treatment has been started.

Once confirmed, appropriate antimalarial treatment must be initiated immediately. Treatment is guided by these main factors: the infecting Plasmodium species, the clinical status of the patient, the organism's life cycle and the drug susceptibility of the infecting parasites, as determined by the geographic area where the infection was acquired. Because the resistance patterns are constantly changing depending on geographic locations.

2. According to the structure:

a) **Aryl-amino-alcohols:** Quinine, quinidine (cinchona alkaloids), mefloquine, halofantrine.

b) **4-aminoquinolines:** Chloroquine, amodiaquine.

c) **Folate synthesis inhibitors:** Type 1: competitive inhibitors of dihydropteroate synthase, sulphones, sulphonamides; Type 2: inhibit dihydrofolate reductase, biguanides like proguanil and chloroproguanil; diaminopyrimidine like pyrimethamine

d) **8-aminoquinolines:** Primaquine

e) **Antimicrobials:** Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones

f) **Peroxides:** Artemisinin (Qinghaosu) derivatives and analogues: artemether, arteether, artesunate, artelinic acid

g) **Naphthoquinones:** Atovaquone

h) **Iron chelating agents:** Desferrioxamine

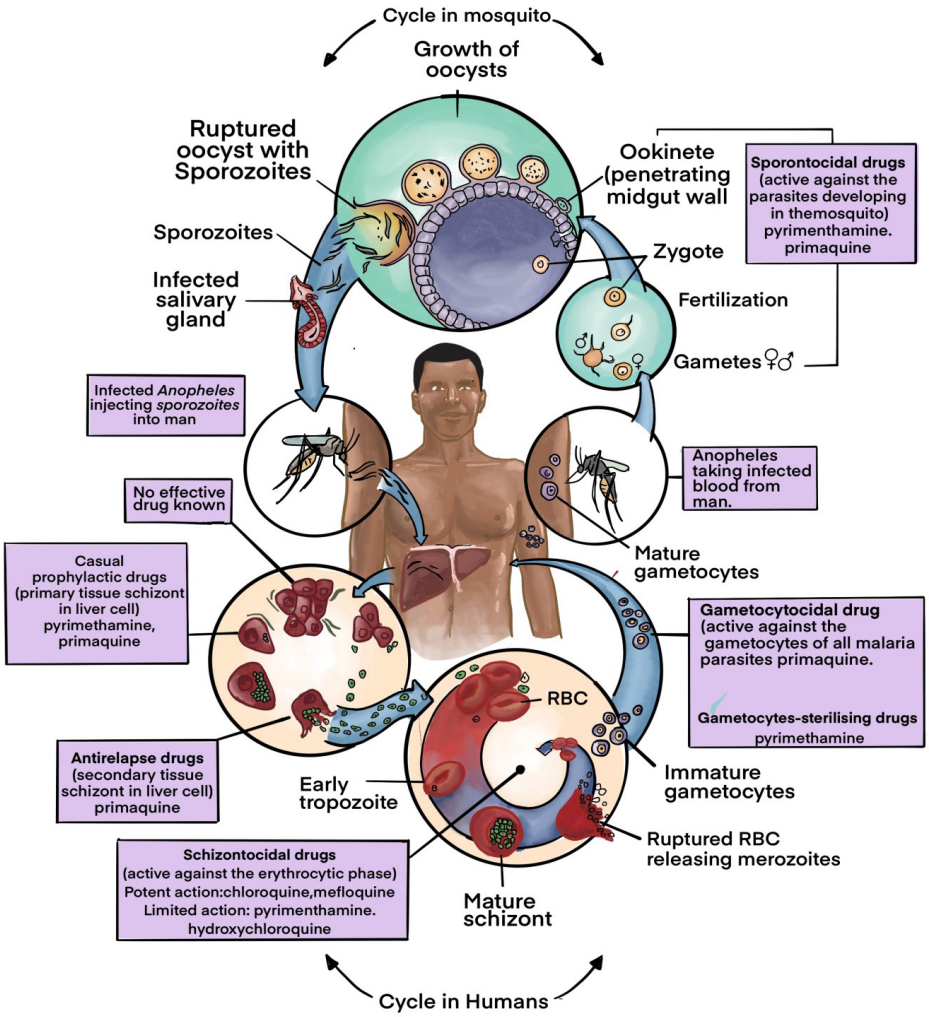


Figure: plasmodium's Life cycle and antimalarial medication

Self-assessment 4.3

1) On which criteria is the selection of drugs for malaria prophylaxis based?
2) When treatment for malaria must be initiated?
3) Antimalarial therapy has three separate objectives, enumerate them.
4) The sporozoites do not respond to antimalarial drugs at all. True or False
5) Why is antimalarial treatment guided by the infecting plasmodium species, the clinical status of the patient, the organism's life cycle and the drug susceptibility of the infecting parasites, considering geographic area?

4.4. Antimalarial drugs prototypes

Learning Activity 4.4

1) During your clinical practice in health center, a senior nurse diagnosed malaria for a patient complaining of fever and arthralgia. As an associate nurse student, list antimalarial drugs you know.

2) A 40 years old female is brought to you with a history of fever for 2 days, chills and anorexia of 1 day. On examination you find that she looks stable, weighs 62 kg, temperature is 39.2 ^{0}C. Other systems are normal. A blood slide reveals plasmodium falciparum ring stage ++

   a) What is the treatment?

   b) If the malaria slide were negative, would you give antimalarial drugs?

CONTENT SUMMARY

Malaria is the most prevalent parasitic endemic disease which is preventable, treatable, and curable. Antimalarial medication is usually given as tablets or capsules. If someone is very ill, it will be given through a drip into a vein (intravenously) in hospital. Many of the same antimalarial medicines used to prevent malaria can also be used to treat the disease.

QUININE

Quinine is the chief alkaloid of cinchona bark (known as 'Fever Bark'), a tree found in South America. Even today, quinine is obtained entirely from the natural sources due the difficulties in synthesizing the complex molecule.

Mechanism of action: Quinine acts as a blood schizonticides although it also has gametocytocidal activity against *P. vivax* and *P. malariae*. Because it is a weak base, it is concentrated in the food vacuoles of *P. falciparum*. It is said to act by inhibiting heme polymerase, thereby allowing accumulation of its cytotoxic substrate, heme.

As a schizonticidal drug, it is less effective and more toxic than chloroquine. However, it has a special place in the management of severe falciparum malaria in areas with known resistance to chloroquine.

Absorption, fate and excretion: Quinine is readily absorbed when given orally or intramuscularly. Peak plasma concentrations are achieved within 1 – 3 hours after oral dose and plasma half-life is about 11 hours. In acute malaria, the volume of distribution of quinine contracts and clearance is reduced, and the elimination half-life increases in proportion to the severity of the illness. Therefore, maintenance dose of the drug may have to be reduced if the treatment is continued for more than 48 hours. The drug is extensively metabolized in the liver and only 10% is excreted unchanged in the urine. There is no cumulative toxicity on continued administration.

Adverse effects: Quinine is a potentially toxic drug. The typical syndrome of quinine side effects is called as cinchonism and it can be mild in usual therapeutic dosage or could be severe in larger doses. Mild cinchonism consists of ringing in the ears (tinnitus), headache, nausea and disturbed vision. Functional impairment of the eighth nerve results in tinnitus decreased auditory acuity and vertigo. Visual symptoms consist of blurred vision, disturbed colour perception, photophobia, diplopia, night blindness, and rarely, even blindness. These changes are due to direct neurotoxicity, although vascular changes may contribute to the problem.

Gastrointestinal symptoms like nausea, vomiting, abdominal pain and diarrhea may be seen. Rashes, sweating, angioedema can occur. Excitement, confusion, delirium are also seen in some patients. Coma, respiratory arrest, hypotension, and death can occur with over dosage. Quinine can also cause renal failure. Massive hemolysis and hemoglobinuria can occur, especially in pregnancy or on repeated use. Hypoprothrombinemia, agranulocytosis are also reported.

Quinine has little effect on the heart in therapeutic doses and hence regular cardiac monitoring is not needed. However it can cause hypotension in the event of overdose. Quinine reduces the excitability of the motor end plate and thus antagonises the actions of physostigmine. It can cause respiratory distress and dysphagia in patients of myasthenia gravis.

Quinine stimulates insulin secretion and in therapeutic doses it can cause hypoglycemia. This can be more severe in patients with severe infection and in pregnancy. Hypoglycemia in malaria may go unnoticed and could even cause death. Therefore, it is advisable to monitor blood glucose levels at least once in 4-6 hours while quinine is administered, especially in severe infection and in pregnancy. Quinine induced hypoglycemia can recur even after administration of 25% or 50% dextrose. In such situations, maintenance with a 10% dextrose infusion is advisable. Resistant hypoglycemia due to quinine can be managed with Injection Octreotide, 50 microgram subcutaneously, every 6 to 8 hours.

Contraindications: Hypersensitivity in the form of rashes, angioedema, visual and auditory symptoms are indications for stopping the treatment. It is contraindicated in patients with tinnitus and optic neuritis. It should be used with caution in patients with atrial fibrillation. Hemolysis is indication for immediately stopping the drug. It is also contraindicated in patients suffering from myasthenia gravis.

Availability: It is available as tablets and capsules containing 300 or 600 mg of the base. It is also available as injections, containing 300 mg /ml.

Quinidine: The anti-arrhythmic drug related to quinine can also be used in the treatment of severe *P. falciparum* malaria. Dose is 10 mg of base / kg by infusion over 1-2 hours, followed by 0.02 mg/kg/min with ECG monitoring.

Chloroquine

Chloroquine is the prototype antimalarial drug, most widely used to treat all types of malarial infections.

Mechanism of action: The mechanism of action of chloroquine is unclear. Being alkaline, the drug reaches high concentration within the food vacuoles of the parasite and raises its pH. It is found to induce rapid clumping of the pigment. Chloroquine inhibits the parasitic enzyme heme polymerase that converts the toxic heme into non-toxic hemazoin, thereby resulting in the accumulation of toxic heme within the parasite. It may also interfere with the biosynthesis of nucleic acids. Other mechanisms suggested include formation of drug-heme complex, intercalation of the drug with the parasitic DNA etc.

Absorption, fate and excretion: 90% of the drug is absorbed from G.I.T and rapidly absorbed from intra muscular and subcutaneous sites. It has a large distribution volume due to extensive sequestration in tissues of liver, spleen, kidney, lung etc. Hence the need for a larger loading dose. Therapeutic blood levels persist for 6-10 days and elimination half-life is 1-2 months. Half of the drug is excreted unchanged by the kidneys, remaining is converted to active metabolites in the liver.

Antimalarial activity: It is highly effective against erythrocytic forms of P. vivax, P. ovale and P. malariae, sensitive strains of P. falciparum and gametocytes of P. vivax. It rapidly controls acute attack of malaria with most patients becoming afebrile within 24-48 hours. It is more effective and safer than quinine for sensitive cases.

Adverse effects: Chloroquine is a relatively safer antimalarial. At therapeutic doses, it can cause dizziness, headache, diplopia, disturbed visual accommodation, dysphagia, nausea, malaise, and pruritus of palms, soles and scalp. It can also cause visual hallucinations, confusion, and occasionally frank psychosis. These side effects do not warrant stoppage of treatment. It can exacerbate epilepsy.

When used as prophylactic at 300 mg of the base/ week, it can cause retinal toxicity after 3-6 years (i.e. after 50-100 g of chloroquine). Intra muscular injections of chloroquine can cause hypotension and cardiac arrest, particularly in children.

Contra indications: Chloroquine should be used with caution in patients with hepatic disease, (even though it is not hepatotoxic per se, it is distributed widely in the liver and is converted to active metabolites there; hence the caution), severe gastro intestinal, neurological or blood disorders. The drug should be discontinued in the event of such problems during therapy.

It should not be co-administered with gold salts and phenyl-butazone, because all the three can cause dermatitis. Chloroquine may interfere with the antibody response to human diploid cell rabies vaccine.

Availability: Chloroquine is available as Chloroquine phosphate tablets; each 250 mg tablet contains 150 mg of the base. Chloroquine hydrochloride injection contains 40 mg of the base per ml.

Sulfadoxine+Pyrimethamine

Pyrimethamine and sulphadoxine are very useful adjuncts in the treatment of uncomplicated, chloroquine resistant, *P. falciparum* malaria. It is now used in combination with artesunate for the treatment of P. falciparum malaria. It is also used in intermittent treatment in pregnancy (IPTp).

Antimalarial activity: Pyrimethamine inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are so essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver. Sulfadoxine inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydropteroic acid. The combination of pyrimethamine and sulfa thus offers two step synergistic blockade of plasmodial division.

Absorption, fate and excretion: Pyrimethamine is slowly but completely absorbed after oral administration and is eliminated slowly with a plasma half-life of about 80-95 hours. Suppressive drug levels may be found in the plasma for up to 2 weeks. The drug is excreted in breast milk.

Sulfonamides are rapidly absorbed from the gut and are bound to plasma proteins. They are metabolised in the liver and are excreted in the urine. They pass through the placenta freely. Sulfadoxine is a long acting sulfonamide with a half-life of 7-9 days.

Toxicity and contraindications: Pyrimethamine can cause occasional skin rashes and depression of hematopoiesis. Excessive doses can produce megaloblastic anemia.

Sulfonamides can cause numerous adverse effects.

Agranulocytosis; aplastic anemia; hypersensitivity reactions like rashes, fixed drug eruptions, erythema multiform of the Steven Johnson type, exfoliative dermatitis, serum sickness; liver dysfunction; anorexia, vomiting and acute hemolytic anemia can also occur.

At the doses employed for malaria, pyrimethamine produces few adverse effects. However, at high doses, such as those used to treat toxoplasmosis, pyrimethamine can produce symptoms of folic acid deficiency.

Effects on the bone marrow manifest as leukopenia, thrombocytopenia, and anemia. Effects on the GI mucosa manifest as ulcerative stomatitis, atrophic glossitis,

pharyngitis, and diarrhea. These responses reverse upon discontinuing treatment, and can be prevented by giving folic acid or folinic acid.

To minimize risk, sulfadoxine should not be given to patients with a history of hypersensitivity to sulfonamides or chemically related drugs, including thiazide diuretics, loop diuretics, and sulfonylurea-type oral hypoglycemics (eg, tolbutamide).

The drug is contraindicated in patients with known hypersensitivity to sulfa, infants below 2 months of age, patients with advanced renal disease and first and last trimesters of pregnancy.

Availability: Pyrimethamine and sulphadoxine is no longer used as a single drug, but only in combination with artesunate.

The Artemisinin Derivatives

Antimalarial activity: Most clinically important artemisinins are metabolised to dihydroartemisinin (elimination half-life of about 45 min), in which form they have comparable antimalarial activity. However, their use in monotherapy is associated with high incidences of recrudescent infection, suggesting that combination with other antimalarials might be necessary for maximum efficacy.

It is the fastest acting antimalarial available. It inhibits the development of the trophozoites and thus prevents progression of the disease. Young circulating parasites are killed before they sequester in the deep microvasculature. These drugs start acting within 12 hours. These properties of the drug are very useful in managing complicated *P. falciparum* malaria. **These drugs are also effective against the chloroquine resistant strains of *P. falciparum***.

Artesunate and artemether have been shown to clear parasitaemias more effectively than chloroquine and sulfadoxine/pyrimethamine. Meta-analysis of mortality in trials indicated that a patient treated with artemether had at least an equal chance of survival as a patient treated with quinine.

It has also been reported that artemisinin drugs cleared parasites faster than quinine in patients with severe malaria but fever clearance was similar. Also, parenteral artemether and artesunate are easier to use than quinine and do not induce hypoglycaemia.

Gametocytocidal action: Artemisinin compounds have been reported to reduce gametocytogenesis, thus reducing transmission of malaria, this fact being especially significant in preventing the spread of resistant strains.

These drugs prevent the gametocyte development by their action on the ring stages and on the early (stage I-III) gametocytes. In studies including over 5000 patients in Thailand, it was shown that gametocyte carriage was significantly less frequent after treatment with artemisinin derivatives than after treatment with mefloquine.

Absorption, fate and excretion: Artemisinin derivatives are absorbed well after intra muscular or oral administration. The drug is fully metabolised and the major metabolite is dihydroartemisinin, which also has Antiparasitic effects. It is rapidly cleared, predominantly through the bile.

Toxicity: Toxic effects have been reported less frequently with the artemisinins than with other antimalarial agents. The most common toxic effects that have been identified are nausea, vomiting, anorexia, and dizziness; these are probably due, in many patients, to acute malaria rather than to the drugs. More serious toxic effects, including neutropenia, anemia, hemolysis, and elevated levels of liver enzymes, have been noted rarely.

Extensive studies in many species showed that intramuscular dosing was more toxic than oral dosing and that, by any route; fat-soluble artemisinins were more toxic than artesunate.

Another concern about artemisinins is embryotoxic effects, which have been demonstrated in animals. Studies from Asia and Africa, including treatment during the first trimester, showed similar levels of congenital abnormalities, stillbirths, and abortions in patients who received and those who did not receive artesunate during pregnancy. Limited data are available on the use of intravenous artesunate for severe malaria during pregnancy.

Availability: Artemisinin is available as its derivatives, artemether and artesunate. The ether derivatives are more soluble in oil and are available as injections for intra muscular use. Artemether is available as injections of 80 mg in 1 ml. Artemether capsules containing 40 mg of the drug are also now available.

Artesunate is an ester derivative that is more soluble in water. The drug is available as a powder. It should be first dissolved in 1 ml of 5% sodium bicarbonate (usually provided with the vial) and shaken for 2-3 minutes.

After it dissolves completely, it is diluted with 5% dextrose or saline (for intravenous use, dilute with 5 ml and for intramuscular use, dilute with 2 ml). Intravenous dose should be injected slowly at a rate of 3-4 ml/minute. It is also available as tablets, each containing 50 mg of the drug.

Rectal artemisinins rapidly eliminate malarial parasites

Resistance: The short half-lives of artemisinins limit the possibility of selection for resistance. However, at present, the likelihood of true artemisinin resistance in malaria parasites is low, and this concern should not prevent the use of intravenous artesunate to treat severe malaria.

ARTEMETHER AND ARTESUNATE

Artemether [Artenam] and artesunate are the most effective drugs available for multidrug resistant falciparum malaria. Both agents are derivatives of artemisinin, a compound isolated from the sweet wormwood plant, Artemisia annua. To be effective, artemether and artesunate must undergo conversion to an active metabolite dihydroartemisinin which kills plasmodia by releasing free radicals that attack the cell membrane. Kill also requires high concentrations of iron, as are found in red blood cells.

Artemether and artesunate are remarkably safe. These drugs can produce transient first-degree heart block, as well as a dose-related decrease in red blood cells and neutrophils. They can also prolong coma and promote fever. However, serious or persistent side effects have not been reported.

Indications

Treatment of severe malaria and initial treatment of uncomplicated malaria, when persistent vomiting precludes oral therapy.

Artesunate is an artemisinin derivative with antimalarial actions much like those of artemether. At this time, artesunate, administered IV, is considered the drug of choice for severe malaria. Artesunate appears to be more effective than IV quinine and safer than IV quinidine.

ARTEMETHER/LUMEFANTRINE

Indications and Efficacy

The combination of artemether (20 mg) and lumefantrine (120 mg), sold as Coartem, is indicated for oral therapy of uncomplicated falciparum malaria.

The combination is not approved for prophylaxis of falciparum malaria, for treatment of severe falciparum malaria, or for prophylaxis or treatment of vivax malaria.

Both artemether and lumefantrine can kill erythrocytic forms of the malarial parasite, but these drugs cannot kill primary or latent hepatic forms.

In clinical trials, artemether/lumefantrine has been highly effective against falciparum malaria: 28 days after a short course of treatment, the cure rate is more than 95%, even against multidrug-resistant P. falciparum. Efficacy against P. vivax is less dramatic.

Mechanism of Action

To be effective, artemether must undergo conversion to an active metabolite dihydroartemisinin which appears to kill plasmodia by releasing free radicals that attack the cell membrane. Lumefantrine probably works like chloroquine, causing death by preventing malaria parasites from converting heme to nontoxic metabolites.

Pharmacokinetics

The kinetics of artemether and lumefantrine differ in three important ways. First, lumefantrine is highly lipophilic, so oral absorption is enhanced by dosing with fatty food. Second, absorption of artemether is relatively rapid (plasma levels peak about 2 hours after dosing), whereas absorption of lumefantrine is delayed (plasma levels peak 6 to 8 hours after dosing). Third, the half-life of artemether is short (1.5 hours), whereas the half-life of lumefantrine is prolonged (100 hours).

Adverse Effects

Artemether/lumefantrine is generally well tolerated. Approximately one-third or more of adults taking this drug experience adverse effects such as headache, anorexia, dizziness, weakness, joint pain, and muscle pain. Among children, the most common adverse effects are fever, cough, vomiting, anorexia, and headache.

Lumefantrine may prolong the QT interval, posing a risk of serious dysrhythmias. Accordingly, artemether/lumefantrine should not be used by patients with electrolyte disturbances (e.g., hypokalemia, hypomagnesemia) or congenital prolonged QT syndrome, or by patients using other drugs that prolong the QT interval (e.g., quinine, erythromycin, and ketoconazole).

Why do we combine Artemether With Lumefantrine?

Compared with lumefantrine, artemether is much more effective. As a result, when the drugs are administered together, most of the benefit comes from artemether.

Why, then, do we combine these drugs?

There are two reasons:

First, adding lumefantrine enhances efficacy. (Because lumefantrine has a much longer half-life than artemether, lumefantrine remains in the body long enough to kill the few parasites not killed by artemether).

Second, adding lumefantrine helps prevent development of resistance to artemether. Why? Because the odds of developing resistance to the two drugs simultaneously are much lower than the odds of developing resistance to artemether alone. Accordingly,

In 2006 the World Health Organization requested that all drug companies stop selling artemisinin-only products and replace them with artemisinin combination therapies (ACTs). Four ACTs are recommended:

- Artemether/lumefantrine [Coartem]
- Artesunate/mefloquine

- Artesunate/amodiaquine
- Artesunate/pyrimethamine/sulfadoxine

N.B: These combinations are indicated only for the treatment of malaria not for prophylaxis.

The other medications used to treat malaria are: Chloroguanide (Proguanil), Halofantrine, **Mefloquine**, **Atovaquone, Pyronaridine, Piperaquine,** Clindamycin, ciprofloxacin, Norfloxacin, azithromycin, **Tetracyclines, Doxycycline** and **Clindamycin.**

SUMMARY OF COMMON DRUGS USED TO TREAT MALARIA

	First line treatment	**alternative:**
Simple malaria	Artemether 20 mg and Lumefantrine 120 mg, twice a day for 3 days Paracetamol: 15 mg/ kg TID	Oral Quinine sulphate 10 mg / kg TID for 7 days;
Simple malaria with minor digestive symptoms	Artesunate IV: 2.4 mg/ kg (time = 0) then at 12 hour, then daily thereafter	**In children:** Quinine dihydrochloride (Salt) intra-rectal: 15 mg/kg body In adult: oral Quinine sulphate 10 mg / kg TID for 7 days
Severe malaria	Artesunate IV 2.4mg/ kg IV (time = 0), then at 12h and 24h, then once a day for three days. Then continue with artemether 20mg and Lumefantrine 120 mg, twice a day for 3 days	**Quinine IV:** Loading dose of 20 mg/kg (do not exceed 1200 mg) Followed by a maintenance dose of 10 mg/kg body weight

Self-assessment 4.4

1) A 32-year-old female student developed fever for last 3 days. She consulted a nearby health center and the health care provider suspect malaria and he asked for blood film for malaria. Results showed plasmodium falciparum and he decided to give quinine. What are the adverse effects that can be associated with quinine at usual therapeutic doses?
2) A patient with a history of malaria presently being treated with chloroquine is admitted to the hospital. What are the side effects should the nurse anticipate at therapeutic doses?
3) True and false questions
   a) The erythrocytic forms are not killed with relative ease whereas the exoerythrocytic (hepatic) forms are very easy to kill. True or false
   b) Tissue schizonticides for causal prophylaxis: These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. True or false
   c) Tissue schizonticides for preventing relapse: These drugs that do not act on the hypnozoites of P. vivax and P. ovale in the liver that cause relapse of symptoms on reactivation. True or false
   d) Blood schizonticides: These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. True or false
   e) Gametocytocides: These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. True or false
   f) Sporontocides: These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. True or false

4.5. Antimalarial drug dosage.

Learning Activity 4.5

1) Two different patients were received at the medical clinic. Patient A was diagnosed for simple malaria and patient B diagnosed for simple malaria on first term pregnancy. Physician recommends quinine tablets as treatment for patient B and Coartem for patient A.
   a) The patient B who received quinine weighs 60 kilograms. Using pharmacology book and internet, and discuss the dosage the healthcare provider will follow while prescribing quinine injection for patient B.
   b) The patient A who received coartem weighs 30 kilograms. Using pharmacology book and internet, and discuss the dosage the healthcare provider will follow while prescribing coartem for patient A.

CONTENT SUMMARY

Our goal in this lesson is to describe the antimalarial drug dosagecalculation.

CHLOROQUINE

Chloroquine phosphate [Aralen] is available in tablets (250 and 500 mg) for oral administration.

Adult: Malaria

Prophylaxis

Indicated for prophylaxis of malaria in geographic areas where resistance to chloroquine is not present; 500 mg (300 mg base) weekly on the same day each week; begin 1-2 weeks before travel, during travel, and for 4 weeks after leaving endemic area.

Treatment

Indicated for acute attacks of malaria due to P. vivax, P. malariae, P. ovale, and susceptible strains of P. falciparum.

Acute attack

- 1 g (600 mg base) PO, THEN
- 500 mg (300 mg base) PO after 6-8 hr THEN
- 500 mg (300 mg base) PO at 24 hr and 48 hr after initial dose

Total dose of 2500 mg (1500 mg-base) in 3 days

Pediatric: Malaria

Prophylaxis

Indicated for prophylaxis of malaria in geographic areas where resistance to chloroquine is not present; 5 mg/kg PO q1 week, not to exceed 500 mg (300 mg base), on the same day each week; begin 1-2 weeks before travel, during travel, and for 4 weeks after leaving endemic area.

Treatment

Indicated for acute attacks of malaria due to P. vivax, P. malariae, P. ovale, and susceptible strains of P. falciparum for adults, infants, and children

- **Acute attack**

Note: Dosing is based chloroquine base; chloroquine phosphate 16.6 mg is equivalent to 10 mg chloroquine base

- **First dose:** 10 mg base/kg (not to exceed 600 mg base/dose)
- **Second dose:** (6 hr after first dose) 5 mg base/kg (not to exceed 300 mg base/dose)

- **Third dose:** (24 hr after first dose): 5 mg base/kg (not to exceed 300 mg base/dose)
- **Fourth dose:**(36 hr after first dose): 5 mg base/kg (not to exceed 300 mg base/dose)

Total dose of 25mg base/kg

QUININE

Dose:

Oral: 10 mg/kg 8 hourly for 7 days.

Intra venous: 20 mg of salt/kg in 10 ml/kg isotonic saline or 5% dextrose over 4hours, then 10 mg of salt/kg in saline or dextrose over 4 hours, every 8 hours until patient is able to take orally or for 5-7 days.

Intra muscular: 20 mg/kg stat, followed by 10 mg/kg 8 hourly by deep intra muscular injections for 5-7 days.

Quinine dihydrochloride IR (intra-rectal) for children: 15 mg per kg body weight diluted in 4 ml of distilled water or physiological solution and administered rectally with a 5-ml syringe every eight hours. Note: If the drug is ejected during the first 10 minutes following its administration, administer other half dose.

Quinine dihydrochloride IV administration (Children and adults):

In infusion, it is administered as 10 mg per kg body weight per dose, diluted in 5 to 10 ml of 5% or 10% glucose per kg body weight, every eight hours. If the patient's condition does not improve within 24 hours of treatment, refer patient to the nearest district hospital.

Table 4.5.1 showing dosage of Oral quinine in function of weight or age

Weight(kg)	Age	N° of tablets of 300mg/ intake
<10	<1year	¼ of tablet
10-14	1-3years	½ of tablet
15-18	4-6years	¾ of tablet
19-30	7-11years	**1 tablet**
31-35	12-15years	**11/2 tablets**
>35	>15years	**2tablets**

DOXYCYCLINE (Monodox/Vibramycin)

100 mg orally daily, 1-2 days before travel and for 4 weeks after return from endemic area.

PYRIMETHAMINE/SULFADOXINE

Pyrimethamine and sulfadoxine are available in a fixed-dose combination **sold as Fansidar**. Tablets contain 25 mg of pyrimethamine and 500 mg of sulfadoxine.

To treat an acute attack of chloroquine-resistant malaria, Fansidar, used in conjunction with quinine, is given as a single dose on the last day of quinine dosing.

Fansidar dosages are as follows:

- Adults, 2 to 3 tablets;
- Children 9 to 14 years, 2 tablets;
- Children 4 to 8 years, 1 tablet;
- Children under 4 years, one-half tablet.

Prevention: 1 tablet orally weekly

ARTEMETHER/LUMEFANTRINE (Coartem)

These combinations are indicated only for treatment of malaria not for prophylaxis. The ACT used most widely is a fixed-dose combination of artemether (20 mg) and lumefantrine (120 mg), sold as Coartem. Patients take a 3 days course, with dosage based on body weight. The cure rate is about 95%, even against multidrug-resistant P. falciparum. To date, there have been no reports of resistance to either component.

Adult/Child >35 kg: PO: 4 tabs of artemether 80 mg/ lumefantrine 480 mg upon diagnosis, then 4 tabs in 8 h, then 4 tabs b.i.d. for 2 days

Adult/Child 25-35 kg: PO: 3 tabs artemether 60 mg with lumefantrine 360 mg in same regimen

Child 15-25 kg: PO: 2 tabs artemether 40 mg with lumefantrine 240 mg in same regimen

Child 5-15 kg: PO: 1 tab artemether 20 mg with lumefantrine 120 mg in same regimen

Artemether by IM: administered as dose of:

- For children: 3.2 mg per kg body weight immediately after a positive blood smear or positive rapid diagnostic test, followed by 1.6 mg/kg after 12 hours
- For adults: 160 mg IM of artemether immediately after a positive blood smear or a positive rapid diagnostic test and 80 mg after 12 hours.

If the patient's condition does not improve within 24h of treatment, refer the patient to the nearest district hospital. If the patient's condition improves, change to oral Artemether-lumefantrine twice a day for three consecutive days.

Table 4.5.2 Dosage of artemether-lumefantrine (COARTEM^{R}) in function of body weight or age

Weight(kg)	Age	Number of tablets/ intake
5-14	3months-3years	**1**
15-24	3-8 years	**2**
25-34	9-14 years	**3**
>35	>14years	**4**

ARTESUNATE

Artesunate is antimalarial drug indicated for initial treatment of severe malaria; should always be followed by a complete treatment course of an appropriate PO antimalarial regimen (Coartem)

Dosage and duration:

- Child under 20 kg: 3 mg/kg/dose
- Child 20 kg and over and adult: 2.4 mg/kg/dose

One dose given on admission (time = 0), the following dose will be administered at 12h then at 24h, then once a day. Administer parenterally at least 24 hours (3 doses), then, if the patient can tolerate the oral route, change to a complete 3 day course of an artemisinin-based combination. If not, continue parenteral treatment once daily until the patient can change to oral route (without exceeding 7 days of parenteral treatment).

Weight	IV injection artesunate solution 10 mg/ml	IM injection artesunate solution 20 mg/ml
< 3 kg	1 ml	0.5 ml
3 to < 4 kg	1.2 ml	0.6 ml
4 to < 5 kg	1.5 ml	0.8 ml
5 to < 6 kg	2 ml	1 ml
6 to < 8 kg	2.5 ml	1.2 ml
8 to < 10 kg	3 ml	1.5 ml
10 to < 13 kg	4 ml	2 ml
13 to < 15 kg	4.5 ml	2.5 ml
15 to < 17 kg	5 ml	2.5 ml

17 to < 20 kg	6 ml	3 ml
20 to < 25 kg	6 ml	3 ml
25 to < 29 kg	7 ml	3.5 ml
29 to < 33 kg	8 ml	4 ml
33 to < 37 kg	9 ml	5 ml
37 to < 41 kg	10 ml	5 ml
41 to < 45 kg	11 ml	6 ml
45 to < 50 kg	12 ml	6 ml
50 to < 55 kg	13 ml	7 ml
55 to < 62 kg	15 ml	8 ml
62 to < 67 kg	16 ml	8 ml
67 to < 71 kg	17 ml	9 ml
71 to < 76 kg	18 ml	9 ml
76 to 81 kg	20 ml	10 ml

Use a 1 ml syringe graduated in 0.01 ml when the dose required is less than 1 ml. For patients over 25 kg, a second vial must be prepared to obtain the volume needed, a third vial for patients over 50 kg and a fourth vial for patients over 76 kg.

Self-assessment 4.5

1) In urban district of a country highly endemic for malaria, a boy aged 6 years weighing 23 kilograms wakes up in the morning and refuses to eat. He is rather quiet but does not have fever. The mother gives three tablets of artemether-lumefantrine (AL). That day when he returned from school he was apparently well. The AL was stopped. Two days later in the evening, he develops fever and vomiting. The mother then gives another 3 tablets of AL. The following morning, he again refused food, and he had a low-grade fever to touch. The mother decides to take the child to the clinic.

   a) Was the mother right to give the AL? Explain your answer.

   b) If the child had malaria, would the mother have stopped the treatment after the initial first dose of AL when the child was apparently well? Please explain

   c) How would the health care provider manage this patient?

2) Explain how to calculate artesunate dosage to be administered via IV

3) Explain dosage calculation for quinine injection for an adult patient with severe malaria.

4.6. Treatment of simple malaria

Learning Activity 4.6

1) You are a S5 nurse student in the clinical placement at a district hospital, and there is a patient taking coartem. During the nursing round, your colleague from S4 asks a senior nurse why the patient is on Coartem. The senior nurse responds to the student that it is because the patient has been diagnosed with simple malaria and tasks you to deeply give explanation of how to manage simple malaria at the health facility level in Rwanda.
   a) What deep explanation will you provide to your colleague regarding the reason of taking coartem?
   b) Who are in-charge of simple malaria management at the community level?
   c) What drug may be used at the health facility level when coartem is contraindicated?

CONTENT SUMMARY

According to clinical manifestations, malaria is classified into three forms: Simple malaria, Simple malaria with minor digestive symptoms and severe malaria.

I. Treatment of simple malaria

➢ **Information Education and Communication (IEC)at family level:**

Strengthening information, education and communication (IEC):

- Knowledge of the mode of transmission of malaria in Rwanda
- Utilization of long-lasting insecticide treated nets (LLINs) as the principal means of prevention and utilization of other preventive measures
- Membership to the community health insurance scheme as means of ensuring early access to health care.
- Recognition by the family members of the signs of simple malaria, simple malaria with minor digestive symptoms and severe malaria
- Seeking care in a timely manner from a community health worker or the nearest health facility, after reducing fever, if present by using sponging.

➢ **At community level (Community health workers)**

The role of the community health worker is to:

- Sensitize the population on the mode of transmission of malaria in Rwanda

- Sensitize the population on the recognition of the signs of the simple malaria, malaria with minor digestive symptoms and severe malaria
- Sensitize the population on seeking care in a timely manner from a community health worker or the nearest health facility, after reducing fever, if present by using tepid sponging.
- Manage cases of children under five with malaria in accordance with the national guidelines after confirmation using a rapid diagnostic test (RDT), under the framework of CCM (community case management), and when necessary refer to a health facility
- Orient the population to the health facility for appropriate management
- Sensitize the population to the use of the long lasting insecticide treated nets as principal means of prevention, environment hygiene and sanitation as well as other preventive measures
- Participate in other malaria control activities at the community level such as indoor residual spraying campaigns, application of larvicides, etc.

➢ **At the level of the health facility**

It is indicated to prescribe the first line of treatment only after obtaining a positive blood smear or positive rapid diagnostic test. A negative blood smear or rapid diagnostic test excludes the diagnosis of malaria and the administration of an antimalarial. Another cause of the fever should be sought systematically and treated accordingly.

The first line treatment recommended is an artemisinin combination therapy (ACT) of 2 molecules in one tablet. That is: Artemether 20 mg and Lumefantrine 120 mg to be taken preferably during meals.

The combination of artemether – lumefantrine (COARTEM^{R}) is administered orally, twice a day for 3 days.

Important instructions to follow:

- Respect the dose prescribed by the health provider
- Directly observe the administration of the first dose
- Do not exceed the prescribed dose

Table 4.6.1: Posology of artemether-lumefantrine (COARTEM^{R}) in function of body weight or age

Weight(kg)	Age	Number of tablets/ intake
5-14	3months-3years	**1**
15-24	3-8 years	**2**
25-34	9-14 years	**3**
>35	>14years	**4**

- Artemether-lumefantrine is contraindicated
  - In children weighing less than 5 kg;
  - During first trimester of pregnancy,
  - In case of allergy to one of the two drugs in the combination and
  - In cases of severe liver or renal disease.

In such cases, oral quinine sulphate is indicated as 10 mg per kg body weight per dose, taken three times a day over seven consecutive days.

Table 4.6.2: Posology of oral quinine in function of weight or age

Weight(kg)	Age	No of tablets of 300mg/ intake
<10	<1year	¼ of tablet
10-14	1-3years	½ of tablet
15-18	4-6years	¾ of tablet
19-30	7-11years	1 tablet
31-35	12-15years	$1^{1/2}$ tablets
>35	>15years	2tablets

N.B: If there is no improvement after 48 hours of treatment, verify if the patient swallowed the drugs correctly, re-examine the patient carefully and do another peripheral blood smear. If the test is positive, change the treatment to oral quinine sulphate as 10 mg per kg body weight per dose, taken three times a day over seven consecutive days. If the peripheral blood smear is negative, exclude and treat other causes of illness and/or refer the patient to the nearest district hospital.

If there is no improvement after 48 hours of treatment with quinine, refer the patient to the nearest District hospital because there is suspicion of other associated pathologies rather than malaria.

II. The management of simple malaria with minor digestive symptoms

The minimum required criteria for treating simple malaria with minor digestive symptoms at a health facility are the following:

- Qualified and trained staff
- The existence of a continuous system of clinical and paraclinical monitoring of patients, 24 out of 24 hours;
- A laboratory with the capacity to do a peripheral blood smear, rapid diagnostic tests and measure haemoglobin.

The management of simple malaria with minor digestive symptoms is done at the health centre, or when not possible in the district hospital.

The patient must be admitted in the health centre where he/she will receive treatment for 24 hours maximum.

After this period, a clinical and paraclinical re-evaluation is done to assess if the patient can be discharged to go home (if there has been improvement and transition towards simple malaria), or be transferred to the district hospital (in cases where there has been no improvement).

The recommended drugs are artemether IM or quinine IR or quinine in IV infusion if diarrhoea is present.

➢ **Modes of administration of the antimalarials**

Depending on the general status and level of hydration of the patient, drugs may be administered as follows:

1) **Artemether by IM:** administered as dose of:
   - For children:3.2 mg per kg body weight immediately after a positive blood smear or positive rapid diagnostic test, followed by 1.6 mg/kg after 12 hours
   - For adults: 160 mg IM of artemether immediately after a positive blood smear or a positive rapid diagnostic test and 80 mg after 12 hours.

If the patient's condition does not improve within 24h of treatment, refer the patient to the nearest district hospital. If the patient's condition improves, change to oral Artemether-lumefantrine twice a day for three consecutive days.

2) **Quinine dihydrochloride IR (intra-rectal) for children:** 15 mg par kg body weight diluted in 4 ml of distilled water or physiological solution and administered rectally with a 5 ml syringe every eight hours. This dose is justified by the slow absorption of quinine by the rectal mucosa. The drug is administered slowly through the anus, and the buttocks are held together for 5 minutes to prevent a premature reflex ejection of the drug. If the patient's condition does not improve after 24 hours of treatment, refer the patient

to the nearest hospital. If the patient's condition improves, change to oral Artemether-Lumefantrine, twice a day for three consecutive days, or in the case of contraindications to Artemether-Lumefantrine, give oral quinine.

Note:

- If the drug is ejected during the first 10 minutes following its administration, administer other half dose.
- Diarrhoea and anal lesions limit the use of this route of administration.

3) Quinine dihydrochloride IV administration (Children and adults):

In infusion, it is administered as 10 mg per kg body weight per dose, diluted in 5 to 10 ml of 5% or 10% glucose per kg body weight, every eight hours. If the patient's condition does not improve within 24 hours of treatment, refer patient to the nearest district hospital.

If the patient's condition improves, change to oral Artemether-Lumefantrine, twice a day for three consecutive days, or to oral quinine in case of contraindications to Artemether-Lumefantrine.

NB: Whatever the medicine and the mode of administration used, (IM artemether, IR/IV quinine), if the state of health of the patient doesn't improve in 24 hours, do a rapid diagnostic test and refer the patient with the referral note or treatment file, giving detailed information on the treatment provided so far, to the nearest hospital.

➢ **Symptomatic treatment**

In case of diarrhoea and/or vomiting:

- Evaluate and monitor the hydration status of the patient;
- Rehydrate the child with ORS or other available liquids, encourage breast feeding and other modes of feeding and if necessary use a naso-gastric tube;
- Antiemetic should be avoided.

In case of fever, give oral Paracetamol 15 mg/ kg, or any other antipyretic drug as it may be indicated.

N.B. In case of pregnant woman with this type of malaria, the treatment is as follows:

1st trimester of pregnancy: give **Quinine dihydrochloride** in infusion until she is able to take oral quinine and continue oral quinine to complete the totality of 7 days

2nd and 3rd trimester of pregnancy: give Artemether IM or quinine IV infusion until she is able to take oral treatment and pass to oral COARTEM 4 tablets twice a day in 3 days.

Self-assessment 4.6

1) A 38-year-old male with no significant past medical history has returned to Rwanda from traveling to malaria endemic region. He forgot to take chemoprophylaxis for malaria and now presents with fever, chills, rigors, and blood smear test reveals plasmodium. Which therapy should be initiated to this patient?

   a) Coartem

   b) Quinine 648 mg

   c) Mefloquine 250 mg

   d) Quinidine 300 mg

2) A pregnant mother in the first trimester was diagnosed with simple malaria. The fellow student in the clinical placement asks you the reason why quinine was given, and not coartem. What would be your answer to this student?

3) A 10-year-old male patient weighing 28 kilograms is admitted at the health facility. He complains of fever, headache, vomiting, and mild diarrhea. The laboratory exam reveals malaria. The nurse decides to give artesunate, and she tasks to calculate the dose to administer to this patient immediately. How would you calculate this dosage?

4.7. Treatment of severe malaria

Learning Activity 4.7

As an associate nurse student, you are carrying out clinical practice at the health center, and you receive a patient with history of fever, inability to stand still, and chills. On the assessment, the patient is weak with pale palpebral conjunctivae, and you decide to order the laboratory investigations.

The blood smear reveals the plasmodium. In addition, you take the glycaemia which reveals 40 mg/dL. You take a decision to refer the patient to the district hospital.

1) What are the antimalarial medications you may use in pretransfer treatment?

2) What are the minimum tests should the laboratory be able to perform in order to confirm severe malaria?

3) List 2 antibiotic medications used to manage cerebral malaria in Rwanda

CONTENT SUMMARY

The management of severe malaria must be done in either district hospital or the national referral hospital (private or public) as ordered by the ministry of health. The management of severe malaria should be done in either a district hospital or a national referral hospital (private or public) that meets the corresponding requirements of the Ministry of Health.

The minimum required criteria are:

1) Qualified staff, trained in the clinical management of malaria-by-Malaria Unit;
2) The existence of a continuous system of 24 hours clinical and paraclinical follow-up of patients;
3) A laboratory with the capacity to at least do:
   - Peripheral blood smear,
   - Haemoglobin and haematocrit,
   - Blood sugar and
   - Proteinuria
4) Capacity to do a lumbar puncture (recommended in cerebral malaria form);
5) Possibility to transfuse in case of severe anaemia;
6) Possibility to provide oxygen;
7) Availability of the drugs and consumables required for the treatment of severe malaria (IV quinine, 50% and 5% glucose, Phenobarbital, diazepam, antipyretics and furosemide).

➢ Pre-transfer treatment at the health centre

While preparing for the transfer of the patient, urgently administer IM artemether or quinine IR or IV (IV infusion). Depending on the general condition of the patient (weak pulse or not, dehydration or none), the health centre staff will administer, either:

- Quinine, preferably by intravenous infusion as a loading dose of 20 mg per kg body weight to run in 4 hours (not exceeding a total dose of 1200 mg for the loading dose); or
- Quinine by intrarectal route in children, as 20 mg per kg body weight diluted in 4 ml of distilled water or physiological solution, administered with a 5-ml syringe. The drug is gently guided through the anus and the buttocks are held together for 5 minutes to prevent the premature reflex expulsion of the drug. If the drug is expelled within the first 10 minutes following its administration, administration is repeated using half the original dose. Diarrhoea and anal lesion limit the use of this route for the administration of drugs
- Arthemether IM 3.2 mg per kg body weight administered as a single dose before transferring the patient.

Note:

- Regardless of the pre-transfer treatment that is given (loading dose of Quinine or Arthemether), treatment with Quinine in intravenous infusion continues at a dose of 10 mg of quinine per kg body weight diluted in 10ml of 5% or 10% Glucose per kg body weight every 8 hours.
- **For cerebral malaria, administer the first dose of antibiotics:**

For children: Ampicillin 50 mg/kg body weight per dose, four times a day to which is added chloramphenicol 25 mg/ kg body weight per dose, four times a day.

For adults: Ampicillin 1.5 g four times a day and chloramphenicol 1 g four times a day;

Note: The intramuscular use of Quinine is prohibited in all health facilities in Rwanda!!

- In case of hypovolaemia (severe anemia, rapid breathing, coma or systolic BP < 80 mm Hg), start with normal saline or Ringer's lactate infusion in a dose of 20 ml/kg to run for 30 minutes to move the patient out of shock.
- For malnourished children (kwashiorkor or marasmus), give the loading dose of quinine in IV perfusion without fluid replacement (as it is difficult to assess hypovolaemia and dehydration, fluid replacement can increase the risk of circulatory overload).
- The administration of quinine in intravenous infusion is preferable in cases of signs of vital distress (repeated convulsions, coma, respiratory distress, and cardio-vascular shock). In the case where it has been impossible to establish an intravenous line to administer quinine intravenously, use intramuscular artemether or intra-rectal quinine.

➢ **Symptomatic treatment**

If the temperature is higher or equal to 38°C:

- Do sponging;
- Give Paracetamol 15 mg /kg body weight by oral route or suppository form, or any other antipyretic that may be indicated.

To prevent hypoglycaemia (characterized by lack of consciousness, severe weakness):

- Give 20-50 ml of 50% hypertonic serum of glucose by intravenous injection administered over 5-10 minutes in adults; and for children 3 ml/kg body weight of 10% glucose or if not available 1 ml/kg of 50% glucose;
- Or administration of water with 10% sugar per mouth or with nasogastric tube, at a rate of 5 ml/kg for children and 50 -100 ml for the adults.

Water with 10% sugar is readily prepared in the following way: take 100 ml of boiled clean water and add 10 g of sugar or 2 coffee spoons.

In case of convulsions:

- Administer Diazepam 0.5 mg/kg body weight intrarectally for children and 10 mg slow IV for adults;
- If convulsions persist, give Phenobarbital 10-15 mg/kg IM;
- Treat or prevent hypoglycaemia;
- Treat fever if necessary.

Refer the patient to the nearest district hospital or national reference hospital.

➢ **Treatment of the severe malaria in the hospital**

In children and adults

Administer a loading dose of 20 mg/kg body weight of quinine dihydrochloride (do not exceed 1200 mg) diluted in an isotonic solution or 5 or 10% glucose on the basis of 5 to 10 ml/kg body weight to run for 4 hours in IV perfusion. Then run IV glucose 5 or 10% for 4 hours as maintenance drip.

Thereafter, i.e. 8 hours after the beginning of the administration of the loading dose or 4 hours after the beginning of the maintenance drip, administer a maintenance dose of 10 mg/kg body weight of quinine dihydrochloride in infusion, to run for 4 hours. This maintenance dose of quinine will be repeated every 8 hours until the patient can swallow, normally within 48 hours at the most.

If after 48 hours the patient's state doesn't permit the patient to take quinine orally, one may continue the drip of quinine by reducing the doses to 7 mg/kg every 8 hours to run for 4 hours.

Change to oral quinine 10 mg/kg of quinine sulphate every 8 hours as soon as the patient can swallow, to complete the 7 days of treatment or oral Artemether 20 mg and Lumefantrine 120 mg, as recommended for the treatment of simple malaria.

NB: For the patient whose body weight is over 60 kg, give the loading dose and decrease the dose from 1200 mg to 800 mg after, divided into two doses for not exceeding 2000 mg per day,

- The loading dose of quinine is not administered if the patient received quinine in the past 12 hours
- Never exceed 2 gm of daily dose of quinine.
- For the cerebral form of severe malaria (cerebral malaria or neurological malaria), the association of IV antibiotherapy is recommended namely:
  - Children: (Ampicillin 50 mg/kg /dose 4 times a day, plus Chloramphenicol 25 mg/kg/dose 4 times a day)
  - Adults: (Ampicillin 1.5 g 4 times a day, plus Chloramphenicol 1g 4 times day)

- For the anaemic form of severe malaria antibiotherapy is not indicated.
- The recommended dose for oral quinine is 10 mg Quinine salt per kg body weight every 8 hours for 7 days;
- Quinine Syrup is not nowadays recommended

Self-assessment 4.7

An adult pregnant woman is a worker in a sugar cane company. A week ago she got tired by the end of the day. At home, she developed fever with sweating and she vomited twice. She diagnosed herself as having malaria and she asked her son to bring anti-malarial medication from a nearby pharmacy. She took the drug for 2 days. Five days later she again developed fever, severe headache, nausea and severe weakness. This time, she decided to go to the hospital. On physical exam, the physician noticed conjunctiva pallor and laboratory results showed haemoglobin of 5g/dL with positive blood smear. The physician diagnosed the patient as having severe malaria, anaemic form.

1) Discuss how to manage this patient at the hospital.
2) Is it advisable to give the antibiotic to this patient?

4.8. Treatment of malaria for pregnant women

Learning Activity 4.8

A health care provider working in the health centre received a call to see a 25-year-old pregnant woman presenting with fever. On examination, the provider couldn't detect any abnormality apart from the axillary temperature of 38.5°C. The health care provider highly suspected malaria, although he thought of other possible diseases. He then requested for the blood smear which showed malaria parasite seen with + and he decided to institute the treatment.

1) What antimalarial medicine (s) would you give a pregnant woman with uncomplicated simple malaria
2) A pregnant woman may never be treated with coartem because it can harm the baby. True or False

CONTENT SUMMARY

The malaria causes many problems to the pregnant women, prevention, early detection and treatment are very important to reduce the mortality and morbidity caused by malaria in pregnant women. This lesson is going to discuss the management of malaria in pregnant women at family level, community level and Health facility.

At the family level

Strengthen IEC on:

- Knowledge of the mode of transmission of malaria in Rwanda.
- Utilisation of long-lasting insecticide treated mosquito nets as principle means of prevention and other preventive measures.
- Membership to the community health insurance schemes as a way of ensuring better access to care.
- Recognition of the signs of simple malaria, simple malaria with minor digestive symptoms and severe malaria by the family members;
- Seeking timely care from the community health care worker or the nearest health facility after lowering fever, if any, using tepid sponging.

At the Community level (Health Animator)

The role of the community health worker is to educate the pregnant woman on:

- The mode of transmission of malaria (mosquito bite);
- The effects of malaria on pregnancy (on the mother and the baby)
- Recognition of the signs of the simple malaria, malaria with minor digestive symptoms and severe malaria, and the ill effects of fever during pregnancy;
- The benefits of sleeping under long lasting insecticide treated nets
- Destruction of breeding sites (stagnant water)
- Seeking health care from the health facility as soon as they feel signs of malaria
- The importance of taking all the drugs as prescribed by the health worker;
- The benefits of 4 ANC contacts.

At the level of the Health facility

To educate the pregnant woman on the preventive measures of malaria in pregnancy during the antenatal consultations:

- What causes malaria and its transmission;
- The effects of malaria on the mother and the baby;
- The advantages of sleeping under long lasting insecticide treated mosquito nets;
- The danger signs of severe malaria;
- The importance of seeking medical care when the symptoms of malaria present;
- The importance of taking a complete dose of antimalarials,
- The benefits of 4 ANC contacts.

Antenatal care

During antenatal care, the health facility staff must do the following to the pregnant woman:

- Give her a long lasting insecticide treated mosquito net;
- Give other components of antenatal care: vaccination, iron, vitamin A and Mebendazole;
- Discuss with her the program of the ANC visits;
- Record on the ANC card, her ANC appointment card, role of LLINs
- Register all illness relate to the pregnancy in the ANC register.

The management of malaria in pregnant women

➢ **Simple malaria**

Because Malaria during pregnancy can aggravate latent anaemia, it is recommended to do a complete clinical exam.

- The first line treatment of malaria in pregnancy is quinine sulphate per os 10 mg/kg/dose, 3 times a day for 7 days during the first trimester of pregnancy.

COARTEM is indicated during the 2nd and 3rd trimesters of pregnancy only.

Note:

- In case of fever, administer paracetamol tablets, 500 mg three times per day;
- Directly observe the woman as she swallows the first dose of antimalarials;
- Respect the dose prescribed by the health provider;
- Record all the information on the ANC card, ANC register and the hospitalization file;
- Give advice on the prevention of the malaria and the necessity to consult in time in case of illness;
- Recommend to the pregnant woman to come back any time if the symptoms persist and/or she develops signs of severe malaria.

➢ **Simple malaria with minor digestive symptoms**

The symptomatology of this type of malaria is similar to the one described earlier in children and adults. The alteration of the general status can be accentuated by the vomiting and other symptoms related to the pregnancy.

- **Curative treatment**

First trimester:

Administer Quinine dihydrochloride in intravenous infusion: 10 mg/kg/dose diluted in 10 ml of 5% or 10% glucose per kg, every eight hours until patient is able to take

drugs orally making sure the treatment does not exceed 24 hours. Once the patient can take orally, complete the remaining quinine 3 X10 mg/kg/day to make 7 days by oral route of drug administration.

Second and third trimester:

Depending on the general status and level of hydration of the patient, drugs may be administered as follows:

Artemether by intramuscular injection:

Administered as dose of 160 mg immediately after the diagnosis followed by 80 mg twelve (12) hours after.

If the patient's condition does not improve within 24 of treatment, refer the patient to the nearest district hospital. If the patient's condition improves, change to oral Artemether-lumefantrine twice a day for three consecutive days.

Quinine dihydrochloride by intravenous administration:

Administered as 10 mg per kg body weight per dose, diluted in 5 to 10 ml of 5% or 10% glucose per kg, every eight hours. If the patient's condition does not improve within 24 hours of treatment, refer the patient to the nearest district hospital.

If the patient's condition improves, change to oral Artemether-Lumefantrine, twice a day for three consecutive days, or to oral quinine in case of contraindications to Artemether-Lumefantrine.

NB: Whatever the medicine and the mode of administration used, (IM artemether, IR/IV quinine infusion), if the state of health of the patient doesn't improve in 24 hours, do a rapid diagnostic test or blood smear and refer the patient with the referral note or treatment file, giving detailed information on the treatment provided so far, to the nearest hospital.

In this case of transfer, the loading dose won't be administered at hospital.

- **Symptomatic treatment**

In case of diarrhoea or vomiting:

- Evaluate and monitor the state of hydration;
- Rehydrate with ORS or other available liquids and even introduce nasogastric tube if necessary;
- Anti-emetics are not recommended.

In case of fever, administer paracetamol 15 mg/kg orally or any other antipyretic that may be indicated.

➢ **Severe malaria in the pregnant woman**

At the health centre

Severe malaria in the pregnant woman is characterized by the same signs as those described earlier for adults and children.

While organizing an emergency transfer, administer loading dose by intravenous infusion of quinine 20 mg/kg body weight in 10 ml of 5% or 10 % dextrose per kg to run for 4 hours (without exceeding 1200 mg);

Artemether, 3.2 mg/ kg can be administered by intramuscular route during the 2nd and 3rd trimester as pre- transfer treatment. It is important to do a complete clinical examination of the woman and to regularly check the vitality of the fœtus.

- **Symptomatic treatment**

If the axillary temperature is ≥ 38°C, give paracetamol 500 mg 3 times per day if the client is able to swallow, or any other antipyretic as it may be indicated.

For the prevention of hypoglycaemia that may be manifested by loss of consciousness, severe asthenia:

- Give 20-50 ml of 50 % of dextrose by intravenous injection to run for 5-10 minutes; or administer water with 10 % sugar orally or by NGT (50 -100 ml).

Preparation of water with 10% sugar

To make 100 ml of water with 10% sugar: take 100 ml of clean water and add to it 10 g (also equivalent to 2 teaspoons) of sugar.

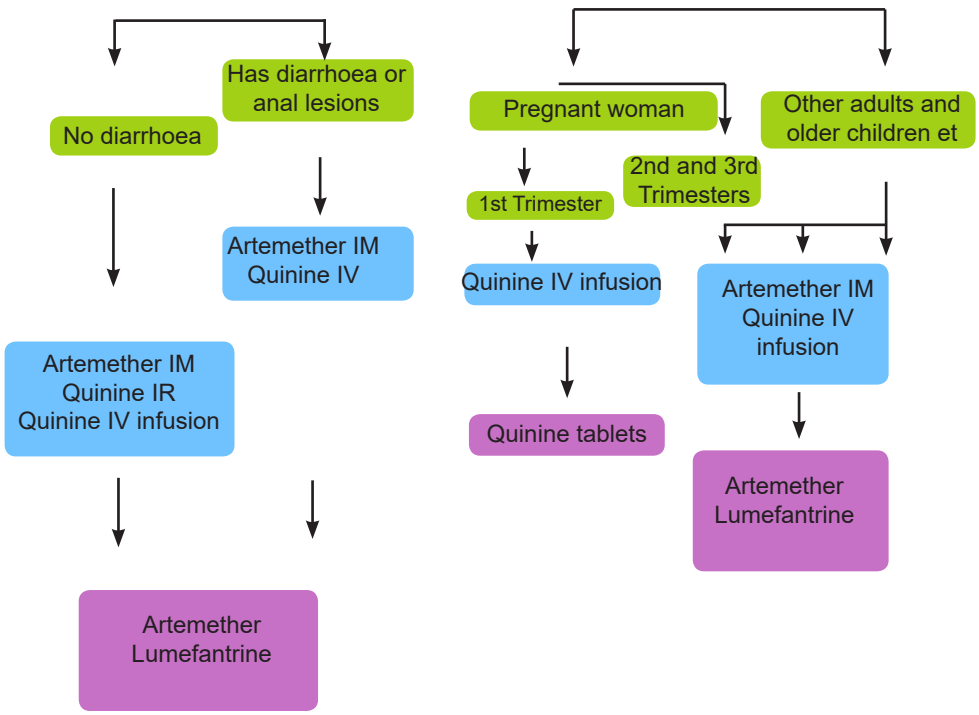
- In case of convulsions:
  - Administer diazepam, 10 mg IV slow; and if convulsions persist, administer diazepam, 10 mg in 500 ml of 5 % glucose to run slowly.
  - Treat or prevent hypoglycaemia;
  - Treat the fever if necessary;
  - Fill in the transfer card correctly and clearly,
  - Record all the necessary information in the register and the ANC card;
  - Refer the patient immediately to the nearest district or national reference hospital.

At the hospital

The treatment of severe malaria in pregnant women at the hospital level is the same as in others adults. Some complications are more frequent in pregnant women and require a particularly close monitoring. These include hypoglycaemia, respiratory distress and severe anaemia.

NB: It is important to do close obstetrical follow-up in general and monitoring of the fetal vitality in particular.

Choice of antimalarial drugs for the treatment of simple malaria with minor digestive symptoms



Self-assessment 4.8

1) An adult pregnant woman patient was admitted to the hospital because of malaise, myalgia, abdominal pain, and high fever. The recent history of the patient was significant for two paroxysmal attacks of chills, fever, and vomiting. Physical examination revealed an acutely ill patient and examination of a stained blood specimen revealed ring like and crescent-like forms within the RBCs reflecting malaria disease.

   a) Discuss curative treatment for pregnant woman suffering from malaria with minor digestive symptoms in the first trimester

   b) Discuss curative treatment for pregnant woman suffering from malaria with minor digestive symptoms in the second and third trimesters.

   c) Discuss treatment for pregnant woman suffering from malaria with minor digestive symptoms in symptomatic treatment.

4.9. Non-malarial antiprotozoal medications (miscellaneous antiprotozoals)

Learning Activity 4.9

A 35-year-old woman presents with a history of diarrhea and abdominal pain for the past 3 days. You learnt that she recently had a trip in areas with poor sanitation, and swallowed considerable amounts of river water. Her relative 30 years old man also presents with a history of diarrhea and abdominal pain for past 2 days after eating unfamiliar food during the trip. The first patient is diagnosed with giardiasis after laboratory exams. The second patient is diagnosed with amebiasis, and treatment should begin after obtaining appropriate specimens.

a) List at least three examples of drugs that can be used in the management of the condition for the first patient with giardiasis.

b) List at least three examples of drugs that can be used in the management of the condition for the second patient with amebiasis.

CONTENT SUMMARY

Several drugs used to treat malaria are also used to treat nonmalarial protozoal infections, including chloroquine, primaquine, pyrimethamine, and atovaquone. Other antiprotozoal drugs normally used against nonmalarial parasites include iodoquinol, metronidazole, paromomycin, and pentamidine.

Use of other antiprotozoal agents may result to these adverse effects:

- **CNS:** headache, dizziness, ataxia, loss of coordination, peripheral neuropathy
- **GI:** nausea, vomiting, diarrhea, unpleasant taste, cramps, changes in liver function
- **Superinfections**

The following are drug-drug interactions involved in the use of other antiprotozoal agents:

- Alcohol: severe adverse effects with tinidazole and metronidazole. Avoid alcohol for at least 3 days after treatment.
- Oral anticoagulants: increased bleeding with metronidazole and tinidazole
- Disulfiram: increased psychotic reactions with metronidazole and tinidazole. Two weeks should elapse between tinidazole therapy and start of disulfiram.

AMEBIASIS

It is an intestinal infection caused by Entamoeba histolytica. It is often known as amoebic dysentery. The disease is transmitted through fecal-oral route. Amebiasis is characterized by mild to fulminant diarrhea. In worst cases, it is able to invade

extra intestinal tissue. Drugs of choice for amebiasis are iodoquinol, paromomycin, metronidazole, and tinidazole.

- **Metronidazole**

Metronidazole [Flagyl, Protostat, Metric 21], a drug in the nitroimidazole family, is active against several protozoal species, including E. histolytica, G. lamblia, and Trichomonas vaginalis. The drug is also active against anaerobic bacteria.

Therapeutic Uses

Metronidazole is a drug of choice for symptomatic intestinal amebiasis and systemic amebiasis. Because most of each dose is absorbed in the small intestine, metronidazole concentrations in the colon remain low, allowing amebas there to survive.

To kill these survivors, metronidazole is followed by iodoquinol, an amebicidal drug that achieves high concentrations in the colon.

Metronidazole is a drug of choice for giardiasis, and for trichomoniasis in males as well as females. Many anaerobic bacteria are sensitive to metronidazole.

Metronidazole interacts with alcohol. Alcohol should be avoided 24 hours before therapy and at least 48 hours after the last dose due a disulfiram type reaction. Metronidazole decreased absorption of vitamin K from the intestines due to elimination of the bacteria needed to absorb vitamin K, increased plasma acetaldehyde concentration after ingestion of alcohol. Resultat: Alcohol causes a disulfiram-like reaction; action of warfarin may be increased (increased bleeding risk).

Adverse Effects.

Metronidazole produces a variety of untoward effects, but these rarely lead to termination of treatment. The most common side effects are nausea, headache, dry mouth, and an unpleasant metallic taste. Other common effects include stomatitis, vomiting, diarrhea, insomnia, vertigo, and weakness. Harmless darkening of the urine may occur, and patients should be forewarned. Certain neurologic effects (numbness in the extremities, ataxia, and convulsions) occur rarely.

If these develop, metronidazole should be withdrawn. Metronidazole should not be used by patients with active disease of the CNS. Carcinogenic effects have been observed in rodents, but there is no evidence of cancer in humans.

Use in Pregnancy and Lactation.

Metronidazole readily crosses the placenta and is mutagenic in bacteria. However, experience to date has not shown fetal harm in humans. Nonetheless, it is recommended that metronidazole be avoided during the first trimester, and employed with caution throughout the rest of pregnancy.

Metronidazole can be detected in breast milk up to 72 hours after administration. Mothers should interrupt breast-feeding until 3 days after the last dose.

Preparations, Dosage, and Administration

Metronidazole [Flagyl, Protostat, Metric 21] is available in capsules (375 mg), standard tablets (250 and 500 mg), and extended-release tablets (750 mg); in solution for injection (5 mg/mL); and as a powder to be reconstituted for injection.

For protozoal infections, the oral formulations are used. Antibacterial therapy usually requires IV treatment.

Dosages:

- Adults, 500 to 750 mg 3 times a day for 7 to 10 days;
- Children 35 to 50 mg/ kg/day in three divided doses for 7 to 10 days.
- Following treatment with metronidazole, iodoquinol is given for 20 days.

➢ **Tinidazole**

Tinidazole [Tindamax] is an antiprotozoal drug similar to metronidazole. Both agents are nitroimidazoles, and both have similar actions, indications, interactions, and adverse effects.

Tinidazole has a longer half-life than metronidazole, and hence dosing is more convenient (it's done less often and on fewer days). However, metronidazole is much less expensive.

Therapeutic Uses

Tinidazole is indicated for trichomoniasis in adults, and for giardiasis, intestinal amebiasis, and amebic liver abscesses in adults and children over 3 years of age. Like metronidazole, tinidazole is considered a drug of choice for all of these infections.

Tinidazole has a half-life of 12 to 14 hours, nearly twice that of metronidazole.

Adverse Effects

Adverse effects are like those of metronidazole, although tinidazole is better tolerated. Gastrointestinal effects metallic taste, stomatitis, anorexia, dyspepsia, nausea, vomiting are most common. Like metronidazole, tinidazole carries a small risk of seizures and peripheral neuropathy. If abnormal neurologic signs develop, tinidazole should be immediately withdrawn. In patients with existing CNS disease, tinidazole should be used with caution.

Use in Pregnancy and Lactation

Tinidazole is in FDA Pregnancy Risk Category C: Animal studies show a risk of fetal harm, but no controlled studies have been done in women. Like metronidazole, tinidazole should not be used during the first trimester of pregnancy.

Tinidazole can be detected in breast milk up to 72 hours after administration. Mothers should not breast-feed while taking the drug and for 3 days after.

Drug Interactions

Like metronidazole, tinidazole has disulfiram-like actions, and hence patients should not consume disulfiram itself, alcoholic beverages, or any product that contains alcohol.

Preparations, Dosage, and Administration

Tinidazole [Tindamax] is available in 250- and 500-mg tablets. For patients unable to swallow tablets whole, the tablets may be crushed and mixed with cherry syrup. To minimize GI distress, tinidazole should be taken with food.

Dosages are as follows:

Intestinal amebiasis:

- adults, 2 gm once daily for 3 days;
- children, 50 mg/kg (maximum 2 gm) once daily for 3 days

Amebic liver abscess:

- adults, 2 gm once daily for 5 days;
- children, 50 mg/kg (maximum 2 gm) once daily for 5 days

TRICHOMONIASIS

It is caused by Trichomonas vaginalis, a flagellated protozoan.

A common cause of vaginitis (reddened, inflamed vaginal mucosa, itching, burning, and yellowish-green discharge).

It is usually transmitted through sexual intercourse and Asymptomatic in men

Metronidazole is the traditional drug of choice.

Dosage:

- Adults, either 2 gm just once or 500 mg twice a day for 7 days;
- Children, 5 mg/kg 3 times a day for 7 days.

However, tinidazole is just as effective and somewhat better tolerated but much more expensive.

Tinidazole

Dosage:

- adults, 2 gm once;
- children, 50 mg/kg (maximum 2 gm) once

TRYPANOSOMIASIS

There are two major forms of trypanosomiasis: American trypanosomiasis and African trypanosomiasis. Both forms are caused by protozoal species in the genus Trypanosoma.

American Trypanosomiasis (Chagas' Disease)

Chagas' disease is caused by T.cruzi, a flagellated protozoan. It is passed to humans by common housefly. It is characterized by severe cardiomyopathy.

In its early phase, Chagas' disease can be treated with nifurtimox or benznidazole. Unfortunately, these drugs are less effective against chronic infection.

African Trypanosomiasis (Sleeping Sickness)

African trypanosomiasis, transmitted by the bite of the tsetse fly, is caused by two subspecies of Trypanosoma brucei: T. brucei gambiense, which causes West African sleeping sickness, and T. brucei rhodesiense, which causes East African sleeping sickness.

During the early (hemolymphatic) phase of African trypanosomiasis, pentamidine and suramin are the drugs of choice. (Pentamidine is preferred for disease caused by T. brucei gambiense, and suramin is preferred for disease caused by T. brucei rhodesiense.) During the late (CNS) stage, melarsoprol and eflornithine are drugs of choice. (Either drug can be used against T. brucei gambiense, but only melarsoprol is preferred for T. brucei rhodesiense).

All four drugs pentamidine, suramin, eflornithine, and melarsoprol can produce serious side effects. Treatment is difficult and frequently unsuccessful.

➢ **Benznidazole**

Benznidazole [Rochagan, in Brazil], a relative of metronidazole and tinidazole, is a drug of choice for American trypanosomiasis (Chagas' disease). The adult dosage is 2.5 to 3.5 mg/kg twice daily, and the pediatric dosage is 5 mg/kg twice daily. For adults and children, the duration of treatment is 30 to 90 days.

➢ **Pentamidine**

Target Diseases and Actions.

Pentamidine [Pentam 300, Pentacarinat, NebuPent] is highly effective against West African sleeping sickness, a disease is caused by T. brucei gambiense, and

against pneumocystis pneumonia (PCP), a disease caused by a fungus named Pneumocystis jiroveci (formerly thought to be Pneumocystis carinii). The drug has multiple actions, including disrupting the synthesis of DNA, RNA, phospholipids, and proteins. However, we don't know which of these actions is responsible for antiprotozoal effects.

- **West African Sleeping Sickness**

Pentamidine is given by IM injection to treat sleeping sickness.

Pharmacokinetics

For treatment of active PCP, Pentamidine is administered IM or IV. Equivalent blood levels are achieved with both routes. The drug is extensively bound in tissues. Penetration to the brain and cerebrospinal fluid is poor. Between 50% and 65% of each dose is excreted rapidly in the urine. The remaining drug is excreted slowly, over a month or more.

Adverse Effects Associated with Parenteral Pentamidine

Pentamidine can produce serious side effects when given IM or IV. Caution is needed.

Sudden and severe hypotension occurs in about 1% of patients. The fall in blood pressure may cause tachycardia, dizziness, and fainting. To minimize hypotensive responses, patients should receive the drug while lying down. Blood pressure should be monitored closely.

Hypoglycemia and hyperglycemia have occurred. Hypoglycemia has been associated with necrosis of pancreatic islet cells and excessive insulin levels. The cause of hyperglycemia is unknown. Because of possible fluctuations in glucose levels, blood glucose should be monitored daily.

Intramuscular administration is painful. Necrosis at the injection site followed by formation of a sterile abscess is common.

Some adverse effects can be life threatening when severe. These reactions and their incidences are leukopenia (2.8%), thrombocytopenia (1.7%), acute renal failure (0.5%), hypocalcemia (0.2%), and dysrhythmias (0.2%).

Adverse Effects Associated with Aerosolized Pentamidine

Inhaled pentamidine does not cause the severe effects associated with parenteral pentamidine. The most common reactions are cough (38%) and bronchospasm (15%). Both reactions are more pronounced in patients with asthma or a history of smoking. Fortunately, these reactions can be controlled with an inhaled bronchodilator. They rarely necessitate pentamidine withdrawal.

Preparations, Dosage, and Administration of Pentamidine

West African Sleeping Sickness

Administration of pentamidine is by IM injection. The dosage for adults and children is 4 mg/kg/day for 7 days.

- **Suramin**

Actions and Uses

Suramin sodium [Germanin] is a drug of choice for the early phase of East African trypanosomiasis (sleeping sickness); for the late phase of the disease (ie, the stage of CNS involvement), melarsoprol and eflornithine are preferred. Suramin is known to inhibit many trypanosomal enzymes; however, its primary mechanism of action has not been established.

Pharmacokinetics

The drug is poorly absorbed from the GI tract, and hence must be given parenterally (IV). Suramin binds tightly to plasma proteins and remains in the bloodstream for months. Penetration into cells is low. Excretion is renal.

Adverse Effects

Side effects can be severe, and hence treatment should take place in a hospital. Frequent reactions include vomiting, itching, rash, paresthesias, photophobia, and hyperesthesia of the palms and soles. Suramin concentrates in the kidneys and can cause local damage, resulting in the appearance of protein, blood cells, and casts in the urine. If urinary casts are observed, treatment should cease.

Rarely, a shock-like syndrome develops after IV administration. To minimize the risk of this reaction, a small test dose (100 to 200 mg) is administered; in the absence of a severe reaction, full doses may follow.

Preparations, Dosage, and Administration

Suramin sodium [Germanin] is available from the CDC Drug Service. The drug is supplied in 1-gm ampules. Administration is by slow IV infusion. Suramin is unstable, and hence fresh solutions must be made daily. The adult dosage is 1 gm IV on days 1, 3, 7, 14, and 21. The paediatric dosage is 20 mg/kg IV on days 1, 3, 7, 14, and 21. Possible revisions in these dosage recommendations should be obtained from the CDC.

- **Melarsoprol**

Therapeutic Use

Melarsoprol [Arsobal, Mel-B] is a drug of choice for both East African and West African trypanosomiasis (sleeping sickness). The drug is employed during the late

stage of the disease (ie, after CNS involvement has developed). For earlier stages, suramin and pentamidine are preferred.

Mechanism of Action

Melarsoprol is an organic arsenical compound that reacts with sulfhydryl groups of proteins. Antiparasitic effects result from inactivation of enzymes. This same action appears to underlie the serious toxicity of the drug.

Melarsoprol is more toxic to parasites than to humans because it penetrates parasitic membranes more easily than human cells.

Adverse Effects

Melarsoprol is quite toxic, and hence adverse reactions are common. Frequent effects include hypertension, albuminuria, peripheral neuropathy, myocardial damage, and Herxheimer-type reactions. Reactive encephalopathy develops in 10% of patients, and carries a 15% to 40% risk of death.

Preparations, Dosage, and Administration

Melarsoprol [Arsobal, Mel-B] is administered by slow IV injection. The drug is highly irritating to tissues, and hence avoiding extravasation is important. Because of its toxicity, melarsoprol should be administered in a hospital setting. Melarsoprol can be obtained through the CDC Drug Service. The drug is not available commercially.

East African Trypanosomiasis

Treatment for adults and children consists of an initial course (2 to 3.6 mg/kg IV daily for 3 days) followed in 7 days by a second course (3.6 mg/kg IV daily for 3 days), followed in 7 days by a third course (3.6 mg/kg IV daily for 3 days).

West African Trypanosomiasis

The dosage for adults and children is 2.2 mg/kg/day for 10 days.

- **Eflornithine**

Actions and uses

Eflornithine [Ornidyl] is indicated for patients with late-stage African trypanosomiasis (sleeping sickness). The drug is highly effective against T. gambiense (West African sleeping sickness), but only variably active against T. rhodesiense (East African sleeping sickness). In both cases, benefits derive from irreversible inhibition of ornithine decarboxylase, an enzyme needed for biosynthesis of polyamines, which are required by all cells for division and differentiation. Parasites weakened by eflornithine become highly vulnerable to lethal attack by host defenses. Because cells of the host can readily synthesize more ornithine decarboxylase to replace inhibited enzyme, cells of the host are spared. Eflornithine is also available in a

topical formulation, marketed as Vaniqa, for use by women to remove unwanted facial hair.

Pharmacokinetics

Eflornithine is given IV. Once in the blood, the drug is well distributed to body fluids and tissues, including the CNS. Eflornithine has a half-life of 100 minutes and is eliminated largely unchanged in the urine.

Adverse Effects

The most common adverse effects are anemia (48%), diarrhea (39%), and leukopenia (27%). Seizures may occur early in therapy but then subside, despite continued treatment. Because IV administration of eflornithine requires large volumes of fluid, fluid overload may develop over the course of treatment. Eflornithine can also cause hair loss. In fact, the drug is now available for topical use to remove facial hair.

Preparations, Dosage, and Administration

Eflornithine is supplied as a concentrated solution (200 mg/mL in 100-mL vials) and must be diluted for IV infusion. To treat West African sleeping sickness in adults and children, the dosage is 100 mg/kg IV 4 times a day for 14 days.

- **Nifurtimox**

Therapeutic Use

Nifurtimox [Lampit] is a drug of choice for American trypanosomiasis (Chagas' disease). The drug is most effective in the acute stage of the disease, curing about 80% of patients. Chronic disease is less responsive.

Pharmacokinetics

Nifurtimox is well absorbed from the GI tract and undergoes rapid and extensive metabolism. Metabolites are excreted in the urine.

Adverse Effects

Therapy is prolonged, and significant untoward effects occur often. Gastrointestinal effects (anorexia, nausea, vomiting, abdominal pain) and peripheral neuropathy are especially common. Weight loss resulting from GI disturbance may require treatment to stop. Additional common reactions include rash and CNS effects (memory loss, insomnia, vertigo, headache). In people with a deficiency of glucose-6-phosphate dehydrogenase, nifurtimox can cause hemolysis.

Preparations, Dosage, and Administration

Nifurtimox [Lampit] is supplied in 100-mg tablets. In the United States, the drug is available only from the CDC Drug Service. The adult dosage is 8 to 10 mg/kg/day

(in three or four doses) for 90 to 120 days. For young children (ages 1 through 10 years), the dosage is 15 to 20 mg/kg/day (in four doses) for 90 to 120 days. For older children (ages 11 to 16 years), the dosage is 12.5 to 15 mg/kg/day (in four doses) for 90 to 120 days.

PNEUMOCYSTOSIS

It is caused by Pneumocystis jirovecii (formerly Pneumocystis carinii), used to be classified as a protozoal infection; however, it is now classified as fungal infection. It is a common infection that complicates HIV and AIDS. It is discussed in this chapter, as opposed to the antifungal, because antifungal drugs are not effective to treat it.

For therapy of PCP, pentamidine is given parenterally and by inhalation. Parenteral therapy is used to treat active PCP. In contrast, inhalational therapy is used to prevent PCP in high-risk HIV positive patients, defined as patients with (1) a history of one or more episodes of PCP or (2) peripheral CD4 lymphocyte counts below 200 cells/mm3. Bronchospasm or cough is more likely to occur when inhaled treatments of pentamidine are given.

Pentamidine isethionate for injection [Pentam 300, Pentacarinat] is supplied in 300-mg, single-dose vials.

For treatment of active PCP, the dosage for adults and children is 3 to 4 mg/kg IV daily for 2 to 3 weeks. Administration must be done slowly (over 60 minutes).

Pentamidine isethionate aerosol [NebuPent] is used for prophylaxis of PCP in patients with AIDS. The dosage is 300 mg once every 4 weeks. Administration is performed with a Respirgard II nebulizer by Marquest. Solutions should be freshly prepared.

TOXOPLASMOSIS

Toxoplasmosis is caused by infection with Toxoplasma gondii, a protozoan of the class Sporozoa. The treatment of choice is pyrimethamine plus sulfadiazine.

- **Pyrimethamine**

Pyrimethamine [Daraprim], combined with sulfadiazine, is the treatment of choice for toxoplasmosis. Pyrimethamine (combined with sulfadoxine) is also used to treat malaria. For toxoplasmosis, the adult dosage is 25 to 100 mg PO daily for 3 to 4 weeks. The pediatric dosage is 2 mg/kg PO daily for 2 days, followed by 1 mg/kg PO daily for 4 weeks.

For adults and children, each dose of pyrimethamine should be accompanied by 10 mg of folinic acid (to reduce side effects). In addition, the regimen must include sulfadiazine: for adults, 1 to 1.5 gm 4 times a day for 3 to 4 weeks; for children, 100 to 200 mg/kg/day for 3 to 4 weeks.

GIARDIASIS

Giardiasis is an infection with Giardia lamblia, also known as G. duodenalis. Transmission is through contaminated water or food, and trophozoites.

Characterized by diarrhea, rotten egg-smelling stool, and pale and mucus-filled stool. Some patients experience epigastric pain, weight loss, and malnutrition.

Drugs of choice are metronidazole, Tinidazole, and nitazoxanide.

Metronidazole: •adults, 250 mg 3 times a day for 5 days; children, 5 mg/kg 3 times a day for 5 days. (more information on Metronidazole check on amebiasis drugs).

Tinidazole: adults, 2 gm once; children, 50 mg/kg (maximum 2 gm) once

- **Nitazoxanide**

Nitazoxanide [Alinia] is the treatment of choice. The drug is very effective in immunocompetent patients, and may also work in some who are immunosuppressed.

Therapeutic Uses

Nitazoxanide [Alinia] is approved for diarrhea caused by G. lamblia in children and adults. Although we have other effective drugs for giardiasis (eg, metronidazole, tinidazole), nitazoxanide is our first effective drug for cryptosporidiosis. Unfortunately, when used for C. parvum infections, nitazoxanide is only effective in children who are immunocompetent; among children who are immunosuppressed, the drug is no more effective than placebo.

Results in immunocompromised adults may be more favorable: When given to adults with cryptosporidiosis and AIDS, a dosage of 1000 mg twice a day for 14 days cured 67% of patients, compared with 25% of those receiving placebo.

Actions

Nitazoxanide appears to work by disrupting protozoal energy metabolism. Specifically, the drug blocks electron transfer mediated by pyruvate: ferredoxin oxidoreductase, and thereby inhibits anaerobic energy metabolism.

In addition to its activity against C. parvum and G. lamblia, nitazoxanide is active against other enteric protozoa (Isospora belli and Entamoeba histolytica) as well as some helminths, including Ascaris lumbricoides, Ancylostoma duodenale, Trichuris trichiura, Taenia saginata, and Fasciola hepatica.

Pharmacokinetics

Nitazoxanide is well absorbed following oral administration. In the blood, the drug undergoes rapid conversion to its active metabolite, tizoxanide, which then undergoes nearly complete (more than 99.9%) binding to plasma proteins. Tizoxanide levels peak between 1 and 4 hours after nitazoxanide administration, and then decline owing to excretion in the urine, bile, and feces.

Adverse Effects

Nitazoxanide is generally well tolerated. In clinical trials, the most common adverse effects were abdominal pain, diarrhea, vomiting, and headache. However, these effects were just as common in subjects taking placebo.

In some patients, the drug caused yellow discoloration of the sclerae (whites of the eyes), which resolved following drug withdrawal. Nitazoxanide is in FDA Pregnancy Risk Category B: Animal studies show no evidence of impaired fertility or fetal harm.

Drug Interactions

Because nitazoxanide is highly protein bound, it might interact with other agents that are highly bound. Specifically, nitazoxanide might displace other drugs from their binding sites, thereby increasing their effects and, conversely, other highly bound agents could displace nitazoxanide, thereby increasing its effects.

Preparations, Dosage, and Administration

Oral Suspension

Nitazoxanide oral suspension [Alinia] is indicated for diarrhea caused by G. lamblia or C. parvum in children ages 1 through 11 years, and for diarrhea caused by G. lamblia (but not C. parvum) in adults. Nitazoxanide is supplied as a pink powder that, when mixed with 48 mL of water, forms a strawberry-flavored, 20-mg/mL suspension. Administration is done with food. The suspension may be stored at room temperature for 7 days, after which it should be discarded. Dosage depends on age as follows:

- For children ages 12 to 48 months, give 100 mg (5 mL) every 12 hours for 3 days.
- For children ages 4 to 11 years, give 200 mg (10 mL) every 12 hours for 3 days.
- For patients 12 years and older, give 500 mg (25 mL) every 12 hours for 3 days.

Nitazoxanide tablets [Alinia] are indicated only for diarrhea caused by G. lamblia, and only for patients at least 12 years old. The dosage is 1 tablet (500 mg) every 12 hours for 3 days. **Administration is done with food**.

LEISHMANIASIS

The term leishmaniasis refers to infestation by certain protozoal species belonging to the genus Leishmania.

It is a disease caused by a protozoan that is passed from sand flies to humans. It is characterized by serious lesions in the skin, viscera, and mucous membranes of host.

For all forms of leishmaniasis, sodium stibogluconate (given IM or IV) is the traditional treatment of choice. Amphotericin B (given IV) is an effective alternative. Miltefosine, an oral agent, is highly curative against visceral leishmaniasis, and probably against cutaneous disease. The drug appears reasonably safe and, owing to oral administration, is more convenient than stibogluconate or amphotericin B, both of which are given parenterally.

- **Sodium Stibogluconate**

Sodium stibogluconate [Pentostam] is a drug of choice for leishmaniasis. The mechanism of action is unknown. The drug is poorly absorbed from the GI tract, and hence must be given parenterally (IM or IV). Sodium stibogluconate undergoes little metabolism and is excreted rapidly in the urine. Although severe side effects can occur, the drug is generally well tolerated. The most frequent adverse reactions are muscle pain, joint stiffness, and bradycardia.

Changes in the electrocardiogram are common and occasionally precede serious dysrhythmias. Liver and renal dysfunction, shock, and sudden death occur rarely. Sodium stibogluconate is supplied in aqueous solution for IM and IV injection. For leishmaniasis, the usual adult and paediatric dosage is 20 mg/kg/day (IM or IV) for 20 to 28 days.

- **Miltefosine**

Miltefosine [Impavido] is the first oral agent for leishmaniasis. The drug was originally developed to treat cancer. Antiprotozoal activity wasn't revealed until miltefosine was tested in cancer patients who also had leishmaniasis. The mechanism underlying benefits in leishmaniasis is unclear.

Studies conducted in India indicate that oral miltefosine is both safe and effective for treating visceral leishmaniasis. Preliminary studies indicate the drug is also highly effective against cutaneous disease.

Because miltefosine is taken by mouth, rather than by injection, the drug is much more convenient than the alternatives, namely, sodium stibogluconate (administered IM or IV) and amphotericin B (administered IV).

Miltefosine is better tolerated than either sodium stibogluconate or amphotericin B. The most common reactions are vomiting (38%) and diarrhea (20%).

Mild hepatotoxicity is seen in some patients, but it resolves during the second week of treatment. Reversible renal damage may also occur. Miltefosine causes fetal abnormalities in laboratory animals, and hence must not be used during pregnancy. Effective contraception is required while taking the drug and for 2 months after.

The recommended dosage for adults and children is 2.5 mg/kg/day for 28 days.

CRYPTOSPORIDIOSIS

Cryptosporidiosis is caused by Cryptosporidium parvum, a protozoan of the subclass Coccidia. Nitazoxanide [Alinia] is the treatment of choice. The drug is very effective in immunocompetent patients, and may also work in some who are immunosuppressed.

Nitazoxanide [Alinia] is approved for diarrhea caused by C. parvum in children only.

Unfortunately, when used for C. parvum infections, nitazoxanide is only effective in children who are immunocompetent; among children who are immunosuppressed, the drug is no more effective than placebo.

Results in immunocompromised adults may be more favorable: When given to adults with cryptosporidiosis and AIDS, a dosage of 1000 mg twice a day for 14 days cured 67% of patients, compared with 25% of those receiving placebo. More information on Nitazoxanide please read on G. lamblia.

Self-assessment 4.9

1) Which drug is used mainly for the management of Pneumocystis jirovecii (formerly Pneumocystis carinii) pneumonia?
   a) Metronidazole (Flagyl)
   b) Pentamidine (NebuPent)
   c) Iodoquinol (Yodoxin)
   d) Chloroquine
2) An adult woman complains of itching and burning around her vagina and foul-smelling vaginal discharge. A nurse suspects trichomoniasis. Which of the following drugs would be appropriate for this patient?
   a) Iodoquinol
   b) Suramin
   c) Sulfadoxine
   d) Metronidazole
3) In which of the following conditions may suramin be indicated?
   a) Trypanosomiasis
   b) Trichomoniasis
   c) Giardiasis
   d) Amebiasis
4) All of the following are the uses of metronidazole, Except:
   a) Amebiasis
   b) Giardiasis
   c) Trichomonas vaginitis
   d) Malaria

4.10. Health Education about Malaria and Amebiasis Treatment

Learning Activity 4.10

1) Why is it important to take a person with symptoms of malaria to the nearest health centre or hospital immediately?
2) Why is it important to finish all medications even if patient starts feeling better?
3) The nurse teaches a patient who is prescribed metronidazole (Flagyl) that it is very important to report which possible adverse effect of the drug to the prescriber?
   a) Darkening of the urine
   b) Metallic taste
   c) Mouth ulcers
   d) Both A and B
4) The following precaution should be advised to the patient who is taking metronidazole
   a) To avoid driving
   b) To get leucocyte count checked every second day
   c) To avoid alcoholic beverages
   d) To avoid fatty/ fried food

CONTENT SUMMARY

A health education interventional is important to take appropriate prevention measures to promote success of treatment and prevention of protozoal diseases. Health education messages can provide information and address a variety of misconceptions regarding the use of antiprotozoal drugs to prevent drug administration's errors.

Patient education is also a basic right of the patients and healthcare members. People should receive instruction in clear language or information on treatment and prevention measures from health care providers by using posters, video clips, radio, and other forms of mass media. Other methods include peer education, mobilization at all levels of public sectors, and school-based programs.

Health education about malaria treatment is guided by many main factors include: the infecting species/parasites, the clinical status of the patient, and the

drug susceptibility of the infecting parasites. People should receive instruction or information on treatment and prevention when traveling to known malaria-endemic regions of the world.

When health care provider is preparing health education about malaria treatment he/she must emphasize on why it is important to take a person with symptoms of malaria to the nearest health care facility immediately.

- Because to be tested for malaria or other illness. The only way to know for sure if you have malaria is to be tested. If you test positively, then you can receive the proper treatment for malaria.
- because to get proper diagnosis and appropriate treatment help health care providers to avoid complications that might lead to serious condition or even death of patient.

Emphasize also on why it is important to finish all medications even if patient start feeling better? Patients should receive instruction to take medication as prescribed and adhere to the full prescription regimen in order to promote success of treatment (kills the parasite in the sick person & saving the life of an infected person), to prevent treatment failure, stops transmission to healthy people, ensure complete cure, on-going protection and will prevent the drug from becoming less effective to malaria infection (development of drug resistance).

Advice the patient to read carefully and follow carefully drugs manufacturer's instructions because every drug differs to another.

Explain to the patient and family members what they should do if they missed a dose.

In the instance that you miss a dose, take it as soon as possible that day. For daily regimes, if you miss the dose completely for that day, skip the missed dose entirely and continue with your next dose. Never take a double dose to make up for a missed dose.

It's important to take your antimalarial medication consistently and for the full course of your prescription. If your medication regime requires you to take it daily, take it at the same time each day (follow dosing orders and instructions as prescribed, with specific attention to the loading doses, subsequent doses, and prophylactic dosing). For weekly regimes, take it on the same day each week.

It's always advisable to purchase all necessary medication prior to your departure. However, in the event that you need antimalarial medication at your destination, you should only purchase medication from a reputable pharmacy.

With antimalarials, encourage adequate dietary and fluid intake while the patient is fighting the infection and taking the medications. Oral doses need to be taken with

water or other fluid. Increase fluids unless contraindicated, because antimalarials concentrate in the liver first.

Never take more than the prescribed dose. Taking too much quinine can cause serious problems. Also, quinine is dangerous if it is taken by a child, so keep the tablets away from children. If you suspect that someone has taken an overdose of quinine or has swallowed some by accident, you must contact a doctor straightaway.

Alternatively, go to the accident and emergency department of a local hospital. Do not delay. Take the container with you, even if it is empty. This helps the doctor to know what patient has been taken. If you are being treated for diabetes, quinine can lower the level of sugar in your blood. Your doctor will be able to advise you about this.

Keep all medicines out of the reach and sight of children. Store in a cool and dry place away from direct heat and light.

Photosensitivity may occur with quinine; provide adequate teaching about the use of sunscreen and sun safety. Sun protection must include coverage against ultraviolet rays.

Educations session on malaria prevention must emphasize on both drug and nondrug (controlling Anopheles Mosquitoes) prevention measures by using the using the ABCD approach (Awareness of risk, Bite prevention, Check whether you need to take malaria prevention tablets and Diagnosis).

For awareness of risk: find out whether the patient is at risk of getting malaria. It's important to visit a health care provider before the travel for advice, check whether it is necessary or need to take preventative malaria treatment depending on the country you are visiting. Some country it is not necessary to take preventative malaria treatment before travelling. Even if you grew up in a country where malaria is common, you still need to take precautions to protect yourself from infection if you're travelling to a risk area.

NB: In area where malaria vaccine is not yet introduced, health care provider has to educate people that nobody has complete immunity to malaria, and any level of natural protection you may have had is quickly lost when you move out of a risk area.

For bite prevention: An Integrated Mosquito Management (IMM) program helps to prevent mosquito bites and transmission of serious vector diseases. To target all phases of the mosquito's life cycle, four approaches are useful in controlling Anopheles Mosquitoes.

1) **Public Education:** we rely on a well-educated public in order to have a successful mosquito control program. Educating the public empowers people to take control of the mosquitoes.

2) **Surveillance:** allows us to detect mosquito species in a given area as well as any changes in populations. With this surveillance, we are able to have more effectively time larvicides applications and more accurately target adulticide activities.

3) **Larval Mosquito Control**: sources of standing water and any newly discovered sites for the presence of mosquito larvae. Eliminating mosquitoes prior to their becoming adults is an important element of controlling malaria and other mosquito-borne diseases because it stops mosquitoes before they acquire the virus and have the opportunity to transmit it to people.

4) **Adult Mosquito Control**: when necessary, adulticide applications are conducted to prevent them from developing resistance; thereby, minimizing the number of applications needed to control the population.

For prevent mosquito bites and transmission of serious vector diseases: avoid mosquito bites by using insect repellent, covering your arms and legs, and using a mosquito net. It's not possible to avoid mosquito bites completely, but the less you're bitten, the less likely you are to get malaria.

To avoid being bitten:

- Stay somewhere that has effective air conditioning and screening on doors and windows. If this isn't possible, make sure doors and windows close properly.
- If you're not sleeping in an air-conditioned room, sleep under an intact mosquito net that's been treated with insecticide.
- Wear light, loose-fitting trousers rather than shorts, and wear shirts with long sleeves particularly during early evening and at night, when mosquitoes prefer to feed.
- Use insect repellent on your skin and in sleeping environments. Remember to reapply it frequently. The most effective repellents contain diethyltoluamide (DEET) and are available in sprays, roll-ons, sticks and creams.

The chemical DEET is not recommended for babies who are less than 2 months old.

DEET is safe for older children, adults and pregnant women if you follow the manufacturer's instructions: use on exposed skin, don't spray directly on to your face, spray into your hands and pat on to your face, avoid contact with lips and eyes, wash your hands after applying, don't apply to broken or irritated skin and make sure you apply DEET after applying sunscreen, not before.

For check whether you need to take malaria prevention tablets: if you do, make sure you take the right antimalarial tablets at the right dose, and finish the course to reduce your chances of getting the disease until vaccine become available for all.

However, antimalarials only reduce your risk of infection by about 90%, so taking steps to avoid bites is also important. Depending on the type you're taking, continue

to take your tablets for up to 4 weeks after returning from your trip to cover the incubation period of the disease.

Check with your health care provider to make sure you're prescribed a medication you can tolerate. You may be more at risk from side effects if you: have HIV or AIDS, have epilepsy or any type of seizure condition, are depressed or have another mental health condition, have heart, liver or kidney problems, take medicine, such as warfarin, to prevent blood clots and use combined hormonal contraception, such as the contraceptive pill or contraceptive patches.

If you've taken antimalarial medication in the past, don't assume it's suitable for future trips. The antimalarial you need to take depends on which strain of malaria is carried by the mosquitoes and whether they're resistant to certain types of antimalarial medication.

NB: In some cases, you may be prescribed emergency standby treatment for malaria before you travel. This is usually if there's a risk of you becoming infected with malaria while travelling in a remote area with little or no access to medical care.

Pregnant women: If you're pregnant, it's advisable to avoid travelling to areas where there's a risk of malaria because a pregnant women have an increased risk of developing severe malaria, and both the baby and mother could experience serious complications. It's very important to take the right prophylactic measures of malaria prevention (both drug and nondrug) if you're pregnant and unable to postpone or cancel your trip to an area where there's a malaria risk. Some of the antimalarials used to prevent and treat malaria are unsuitable for pregnant women because they can cause side effects for both mother and baby.

Malaria is also particularly life-threatening and dangerous to pregnant women and their babies. Malaria is harmful to pregnant women and their babies as the malaria parasite destroys the blood cells and makes women anaemic. Anaemia in the mother and malaria parasites in the placenta can lead to women giving birth to babies early (pre mature) or born very small or die while still in the womb. Babies who are born too early or are very small at birth as less likely to survive and be healthy

For diagnosis: seek immediate medical advice if you have malaria symptoms, including up to a year after you return from travelling. You must seek medical help straight away if you become ill while travelling in an area where malaria is found, or after returning from travelling, even if you've been taking antimalarial tablets.

Malaria can get worse very quickly, so it's important that it's diagnosed and treated as soon as possible.

If you develop symptoms of malaria while still taking antimalarial tablets, either while you're travelling or in the days and weeks after you return, remember to

tell the health care provider which type you have been taking. The same type of antimalarial shouldn't be used to treat you as well.

Health education about amebiasis treatment

When health care provider is preparing health education about malaria treatment he/she must emphasize on appropriate information on treatment and preventive measures.

When an Antiparasitic is prescribed on an outpatient basis; give the patient or family member complete instructions about taking the drug, as well as household precautions that should be followed until the parasite is eliminated from the body.

When developing a patient education plan, be sure to include the following:

- Follow the dosage schedule exactly as prescribed to eradicate the parasite. It is important to explain to the patient how amebiasis treated, once your health care provider has told you that you have amebiasis, you have to take medication. Treatment must be prescribed by a health care provider and specific treatment will vary from person to person.
- Advice the patient to read carefully and follow carefully drugs manufacturer's instructions because every drug differs to another.
- Follow-up stool/urine specimens will be necessary after taking Antiparasitic drugs because this is the only way to determine the success of drug therapy.
- When an infection is diagnosed, multiple members of the family may be infected, and all household members may need to be treated.

It is important to explain to the patient how is amebiasis spread. Amebiasis is transmitted from person to person by the fecal-oral route. The spread of amebiasis can occur if an infected person does not wash their hands properly after going to the bathroom. When people touch objects or eat contaminated food they can get the parasite on their hands and into their mouths. People are infectious as long as the parasite is shed in the stool. The spread of amebiasis can be prevented by public education about the importance of hand hygiene (perform wash hand with soap and water) after defecation and before preparing or eating food.

It is important to ask patient inform if is pregnancy or breast feeding because some antiprotozoal drugs should not be taken by women who are pregnant or breast feeding.

- It is important to wash all bedding and bed clothes once treatment has started.
- Daily bathing (showering is best) is recommended.

Disinfect toilet facilities daily, and disinfect the bathtub or shower stall immediately after bathing. Use the disinfectant recommended by the primary health care provider or use chlorine bleach.

Scrub the surfaces thoroughly and allow the disinfectant to remain in contact with the surfaces for several minutes.

During treatment for a ringworm infection, keep towels and facecloths for bathing separate from those of other family members to avoid the spread of the infection. It is important to keep the affected area clean and dry.

- Wash the hands thoroughly after urinating or defecating and before preparing and eating food. Clean under the fingernails daily and avoid putting fingers in the mouth or biting the nails.
- Food handlers should not resume work until a full course of treatment is completed and stools do not contain the parasite.
- Child care workers should be especially careful of diaper disposal and proper hand washing to prevent the spread of infections.
- Inform the patient taking metronidazole/Tinidazole for a sexually transmitted disease like trichomoniasis to avoid sexual intercourse (as they may become reinfected) until a full course of treatment is completed and samples (urine or/and stool) do not contain the parasite , and advise the client that sexual partners must be treated also.

If you are having giardiasis, you should wash your hands regularly and avoid sharing utensils or towels to prevent the spread of infection among your household members.

Before taking metronidazole, it is important that your health care provider knows: If you are pregnant or breastfeeding.

- If you feel you will be unable to stop drinking alcohol for the duration of your treatment.
- If you have any problems of liver function.
- If you are taking any other medicines
- If you have ever had an allergic reaction to a medicine.

Advise the patient to take the tablets or liquid medicine exactly as prescribed. Space your doses evenly throughout the day, and keep taking the medicine until the course is finished, unless he/she is told to stop by his/her doctor.

- Take each of your doses with a snack or just after eating a meal. Swallow the tablets whole (that is, without chewing or crushing them) with a full glass of water.
- If patient forget to take a dose, advise him/her to take it as soon as he/she remember and try to space the remaining doses evenly throughout the rest of the day. Do not take two doses together to make up for a forgotten dose.

- Advise the patients to avoid drink alcohol while they are on metronidazole and for 48 hours after finishing the course of treatment. This is because drinking alcohol with metronidazole is likely to make you feel very sick (nauseated) and cause other unpleasant effects, such as the sensation of having a 'thumping heart' (palpitations), hot flushes and headache.
- Tell the patients that while they are taking metronidazole their urine may look a darker colour than normal. On its own this is nothing to worry about.
- When the patient is taking metronidazole for amebiasis instruct the patient how to collect stool samples correctly and safely and how to dispose of samples properly.

Self-assessment 4.10

1) What should a patient do when he/she misses a dose of antiprotozoals?
2) What should patient do if she/he runs out or loses an antimalarial medication?
3) What should patient do if he/she thinks that he/she has malaria?
4) A patient tells a nurse that he/she has been infected with malaria in the past and asks a nurse whether he/she still needs to take antimalarial medication?

End of unit assessment 4

1) Which of the following are the factors which determine antimalarial agent efficacy?

   a) Species of the plasmodium

   b) Life-cycle stage-dependencies

   c) Both A and B are correct

   d) Neither of the above

2) Which of the following drugs can cause cinchonism?

   a) Chloroquine

   b) Quinine

   c) Artenisinin

   d) Primaquine

3) A patient is infested by plasmodium ovale and is suffering from repeated relapses. Which ONE of the following drugs can be used to prevent relapses?

a) Chloroquine

b) Quinine

c) Artenisinin

d) Primaquine

4) Neuropsychiatric reactions are most likely to occur in persons treated with:

e) Halofantrine

f) Quinine

g) Mefloquine

h) Artemisinin derivatives

5) All of the following are uses of metronidazole EXCEPT

a) Amebiasis

b) Giardiasis

c) Trichomoniasis

d) Malaria

6) For which of the following diseases is pentamidine the first line drug?

a) Toxoplasmosis

b) Pneumocystis carinii pneumonia

c) Actinomycosis

d) Leishmaniasis

7) Which of the following diseases is treated with metronidazole?

a) Roundworm infestation

b) Hookworm infestation

c) Kala-azar

d) Giardiasis

8) Tick the drug used for toxoplasmosis treatment:

a) Chloroquine

b) Tetracycline

c) Suramin

d) Pyrimethamine

9) Tick the drug used for amebiasis treatment:

a) Nitrofurantoin

b) Tinidazole

c) Pyrazinamide

d) Mefloquine

10) Choose correct answer Treatment of malaria is guided by;

a) The infecting plasmodium species

b) The clinical status of the patient

c) All the responses are correct

d) The stage of the organism's life cycle

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