PHARMACOLOGY

STUDENT BOOK SENIOR 5
ASSOCIATE NURSING PROGRAM

First Edition

FOREWORD

Dear Student

Rwanda Basic Education Board is honoured to present to you this Pharmacology Textbook for Senior five for Associate Nursing program which serves as a guide to competence-based teaching and learning to ensure consistency and coherence in the learning of Pharmacology subject.

The Rwandan educational philosophy is to ensure that you achieve full potential at every level of education which will prepare you to be well integrated in society and exploit employment opportunities. The government of Rwanda emphasizes the importance of aligning teaching and learning materials with the syllabus to facilitate your learning process. Many factors influence what you learn, how well you learn and the competences you acquire. Those factors include the instructional materials available among others. Special attention was paid to the activities that facilitate the learning process in which you can develop your ideas and make new discoveries during concrete activities carried out individually or with peers.

In competence-based curriculum, learning is considered as a process of active building and developing knowledge and meanings by the learner where concepts are mainly introduced by an activity, a situation or a scenario that helps the learner to construct knowledge, develop skills and acquire positive attitudes and values. For effective use of this textbook, your role is to:

- Work on given activities including application activities which lead to the development of skills;
- Share relevant information with other learners through presentations, discussions, group work and other active learning techniques such as role play, case studies, investigation and research in the library, from the internet or from your community;
- Participate and take responsibility for your own learning;
- Draw conclusions based on the findings from the learning activities.

I wish to sincerely extend my appreciation to the people who contributed towards the development of this book, the Ministry of Health, Human Resource for Health Secretariat (HRHS), University of Rwanda, School of Nursing and Midwifery, Higher Learning Institutions and Rwanda Basic Education Board.

Special gratitude goes to University faculty, Nurses, Midwives, Teachers, illustrators, designers, HRH Secretariat Staff and REB Staff who diligently worked to successful completion of this book.

Dr. MBARUSHIMANA Nelson

Director General of Rwanda Basic Education Board

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Head of Curriculum, Teaching and Learning Resources Department / REB

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UNIT 1: ANTIBIOTICS

Key Unit competence:

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

Introductory activity 1.0

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?

1.1. Definition of antibiotics and key concepts

Learning Activity 1.1

1) Read the scenario below:

A 37-year-old female patient is on drugs that she takes 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.

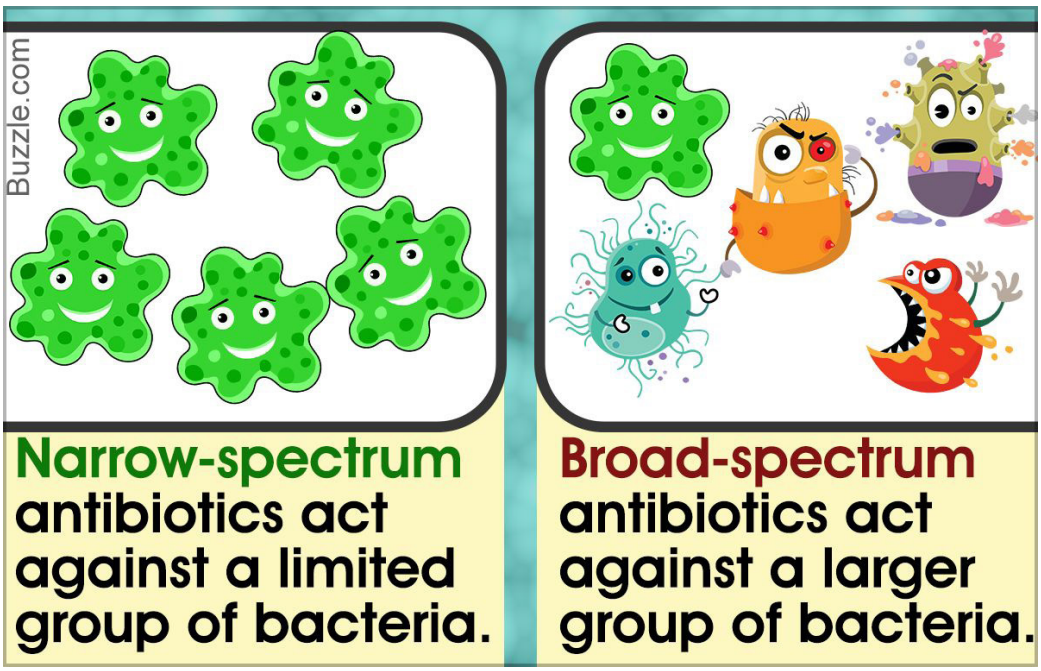
“Bacteriostatic” refers to the ability of the agent (antibiotic) to prevent the growth of bacteria while “bactericidal” is the ability of the agent to kill bacteria.

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 1.1

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?

1.2. Ideal antibiotics and Mechanism of action of antibiotics

Learning Activity 1.2

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 1.2

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

1.3. Drug resistance and prevention of antibiotic drug resistance

Learning Activity 1.3

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 1.3

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

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

1.4.1 Introduction to antibiotics

Learning Activity 1.4.1

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.

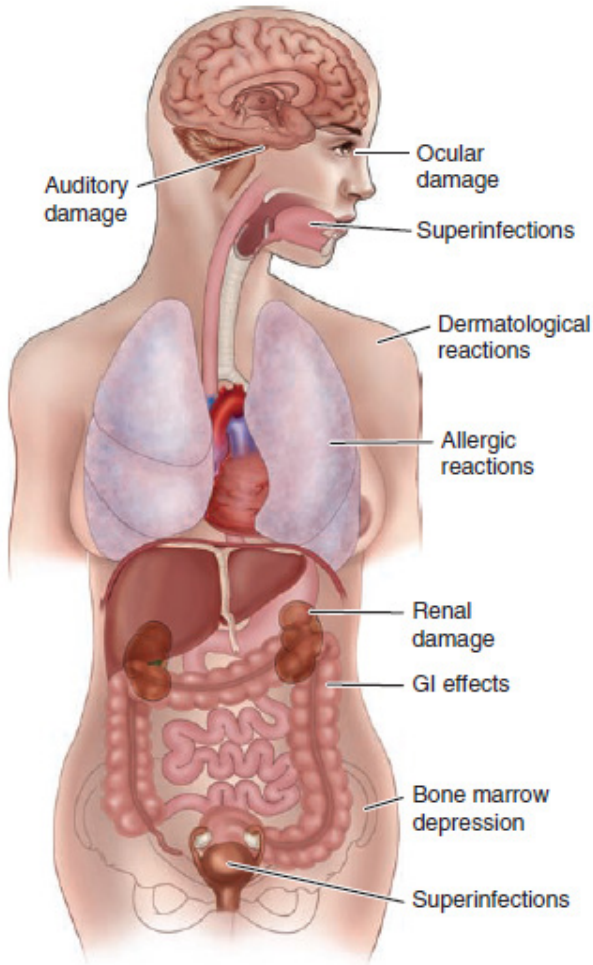


Image on common side effects of antibiotics

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 1.4.1

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.

1.4.2. Class of penicillins and penicillinase resistant antibiotics

Learning Activity 1.4.2

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 1.4.2.1: 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:** 25-45mg/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 1.4.2

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

1.4.3 Class of aminoglycosides

Learning Activity 1.4.3

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 indicated for the treatment of serious infections that are susceptible to penicillin when penicillin is contraindicated. They can be used in severe infections before culture and sensitivity tests have been completed. The aminoglycosides are poorly absorbed from the GI tract but rapidly absorbed after intramuscular injection, reaching peak levels within 1 hour. They have an average half-life of 2 to 3 hours. They are widely distributed throughout the body, cross the placenta and enter breast milk, and are excreted unchanged in the urine.

Aminoglycosides are contraindicated in case of known allergy to any of the aminoglycosides. They are also contraindicated in renal or hepatic disease that could be exacerbated by toxic aminoglycoside effects and that could interfere with drug metabolism and excretion, leading to higher toxicity. Preexisting hearing

loss, which could be intensified by toxic drug effects on the auditory nerve is a contraindication to the use of antibiotics. Ideally, aminoglycosides should be avoided in case of lactation.

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 1.4.3.1: Summary of the prototype aminoglycosides

	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:** 25-45mg/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; Urticaria Serum-sickness like reactions (eg, chills, fever, edema, arthralgia, prostration); Jarisch-Herxheimer reaction reported when treating syphilis; and Pseudomembranous 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 1.4.3

1) Aminoglycosides are primarily used for infections by what type of pathogen?

   a) Gram negative aerobic bacilli

   b) Both Gram negative and Gram-positive bacteria

   c) Yeast and fungi

   d) Gram positive bacteria only

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

   a) Azithromycin

   b) Erythromycin

   c) Streptomycin

   d) Clindamycin

3) The associate nurse considers administration of gentamicin. Which of the following is NOT a side effect of this medication?

   a) Diaphoresis

   b) Ototoxicity

   c) Anorexia

   d) Nephrotoxicity

1.4.4 Class of cephalosporins

Learning Activity 1.4.4

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.1.4.4.1 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 1.4.4

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

1.4.5. Class of fluoroquinolones

Learning Activity 1.4.5

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 1.4.5.1: 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 1.4.5

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?

1.4.6. Class of macrolides

Learning Activity 1.4.6

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 1.4.6.1 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 1.4.6

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
1) All of the following antibiotics are macrolides, **EXCEPT:**
   a) Erythromycin
   b) Clarithromycin
   c) Azithromycin
   d) Streptomycin

1.4.7. Class of tetracyclines

Learning Activity 1.4.7

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 1.4.7.1 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/d intravenous (IV) in two infusions of 1–4 h each or 100–300 mg/d PO Pediatric (>8 y): 4.4 mg/kg/d PO
Dosage form:	IV and oral forms exist

Self-assessment 1.4.7

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?

1.4.8. Class of sulphonamides (sulfonamides)

Learning Activity 1.4.8

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 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 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.

Table1.4.8.1 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 1.4.8

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

1.5. Medications used in treatment of bacterial sexually transmitted diseases and tuberculosis

1.5.1. Medications used in treatment of bacterial sexually transmitted diseases

Learning Activity 1.5.1

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 1.5.1.1: 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 1.5.1

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?

1.5.2. Medications used in treatment of tuberculosis

Learning Activity 1.5.2

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. The standard "short" course treatment for TB is isoniazid, rifampicin (also known as rifampin in the United States), pyrazinamide, and ethambutol for two months, then isoniazid and rifampicin alone for a further four-month period. The patient is considered cured at six months (although there are still some cases of relapse rate of about 2 to 3%). For latent tuberculosis, the standard treatment is six to nine months of isoniazid alone. If the organism is known to be fully sensitive, then treatment is with isoniazid, rifampicin, and pyrazinamide for two months, followed by isoniazid and rifampicin for four months. Ethambutol needs not be used. However, ethambutol is always part of the initial treatment of tuberculosis in Rwanda. Using the drugs in combination helps to decrease the emergence of resistant strains and to affect the bacteria at various phases during their long and slow life cycle.

First line anti-tuberculous drug names have a standard three-letter and a single-letter abbreviation: Ethambutol is EMB or E; Isoniazid is INH or H; Pyrazinamide is PZA or Z and Rifampicin is RMP or R. Drug regimens are similarly abbreviated in a standardized manner. The drugs are listed using their single letter abbreviations (in the order given above, which is roughly the order of introduction into clinical practice).

A prefix denotes the number of months the treatment should be given for; a subscript denotes intermittent dosing (so 3 means three times a week) and no subscript means daily dosing.

Most regimens have an initial high-intensity phase, followed by a continuation phase (also called a consolidation phase or eradication phase): the high-intensity phase is given first, then the continuation phase, the two phases divided by a slash. So, **2HREZ/4HR3** means isoniazid, rifampicin, ethambutol, pyrazinamide daily for two months, followed by four months of isoniazid and rifampicin given three times a week.

There are six classes of second-line drugs (SLDs) used for the treatment of TB. A drug may be classed as second-line instead of first-line for one of three possible reasons: it may be less effective than the first-line drugs (e.g.: p-aminosalicylic acid); or, it may have toxic side-effects (e.g.: cycloserine); or it may be unavailable in many developing countries (e.g., fluoroquinolones): Aminoglycosides: e.g., amikacin (AMK), kanamycin (KM); Polypeptides: e.g., capreomycin, viomycin, enviomycin; Fluoroquinolones: e.g., ciprofloxacin (CIP), levofloxacin, moxifloxacin (MXF); Thioamides: e.g. ethionamide, prothionamide; Cycloserine (the only antibiotic in its class); and P-aminosalicylic acid (PAS or P).

In Rwanda, the following are the therapeutic diagrams of tuberculosis treatment:

Primotreatment: 2HREZ7/4HR7 (for a person who suffers from pulmonary tuberculosis for the first time).

Retreatment: 2S7RHZE7/1RHZE7/5RHE7: A person who received TB treatment for some time in the past, and has a positive sputum smear or needs to take/resume antituberculosis drugs again. In this case, injectable streptomycin is added to the therapeutic diagram (protocol) for the first 2 months, administered intramuscularly.

Self-assessment 1.5.2

1) After 5 months of tuberculosis treatment in the learning activity 1.6.2, the patient still has positive sputum smear that reveals tuberculosis bacteria.

The healthcare personnel decide that such patient requires antituberculosis retreatment, and the treatment is immediately started.

As the relative, you need to give clear details on the drugs to receive, with focus on the additional drugs, their mode of administration, and for how long these drugs will be taken.

Referring to the data above, answer the following questions:

a) Which drug will be added on the usual tuberculosis primo-treatment drugs?

b) What is the route of administration for the added drug?

c) For how long will the added drug be given to the patient?

1.6. End unit assessment

End of unit assessment

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 2: ANTHELMINTIC (ANTIHELMINTHIC) DRUGS

Key Unit Competence

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

Introductory activity 2.0

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?

2.1. Introduction to anthelmintic drugs and deworming

Learning Activity 2.1

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 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 2.1

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

2.2. Anthelmintic medications

Learning Activity 2.2

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 Dosages:

Dosage Considerations – Should be Given as Follows:

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

Pediatric 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 2.2

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

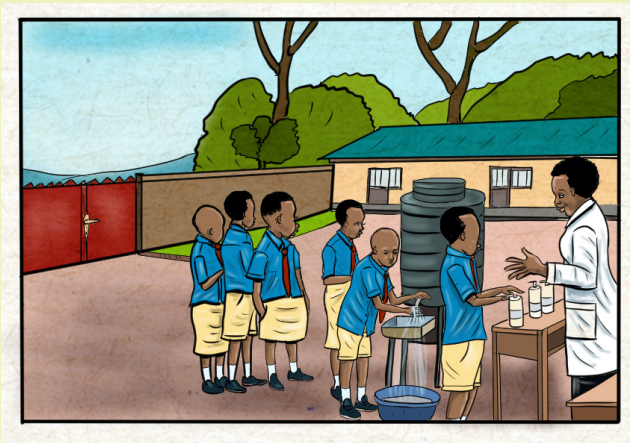
   b) Albendazole dissolves better in water, and drinking a lot of water speeds up its absorption

   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.

2.3. National Guidelines for Deworming and WHO Community Deworming

Learning Activity 2.3



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 2.3

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?

2.4. End unit assessment

End of unit assessment

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 3: ANTIPROTOZOAL DRUGS

KEY UNIT COMPETENCE

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

Introductory activity 3.0

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?

3.1. Definition and Classification of antiprotozoal medications

Learning Activity 3.1

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 3.3.1: 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 3.1

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.

3) Select the drugs you feel the physician is likely to prescribe for patient A

a) Chloroquine,

b) Artemisinin,

c) Amoxicillin

d) Metronidazole

4) Select the drugs you feel the physician is likely to prescribe for patient B

a) Chloroquine,

b) Artemisinin,

c) Pentamidine

d) Nitazoxanide

5) Select the drugs you feel the physician is likely to prescribe for patient C

a) Artemisinin,

b) Metronidazole

c) Chloroquine

d) Suramin

3.2. Plasmodium's life cycle

Learning Activity 3.2

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 39.20 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 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 h 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).

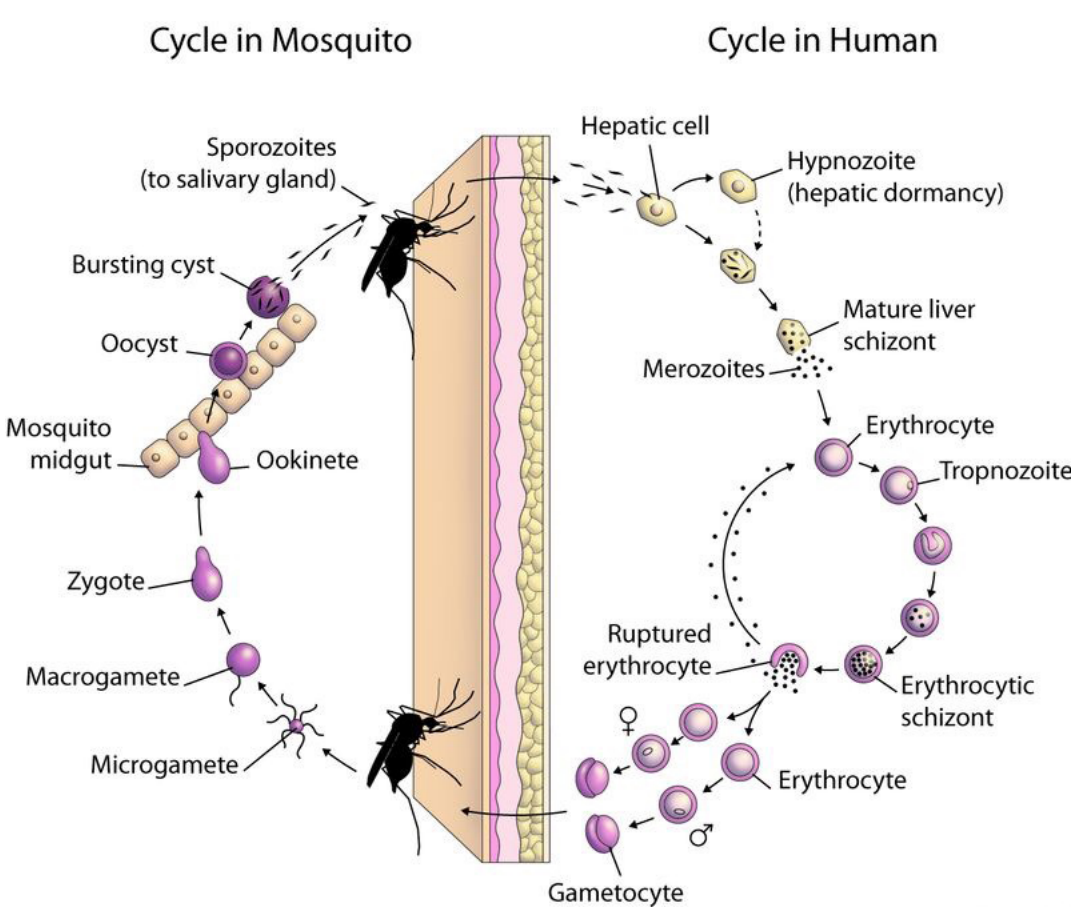


Figure 1: Plasmodium's life cycle

Self-assessment 3.2

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 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

3.3. Antimalarial medications

Learning Activity 3.3

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.

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 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.

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

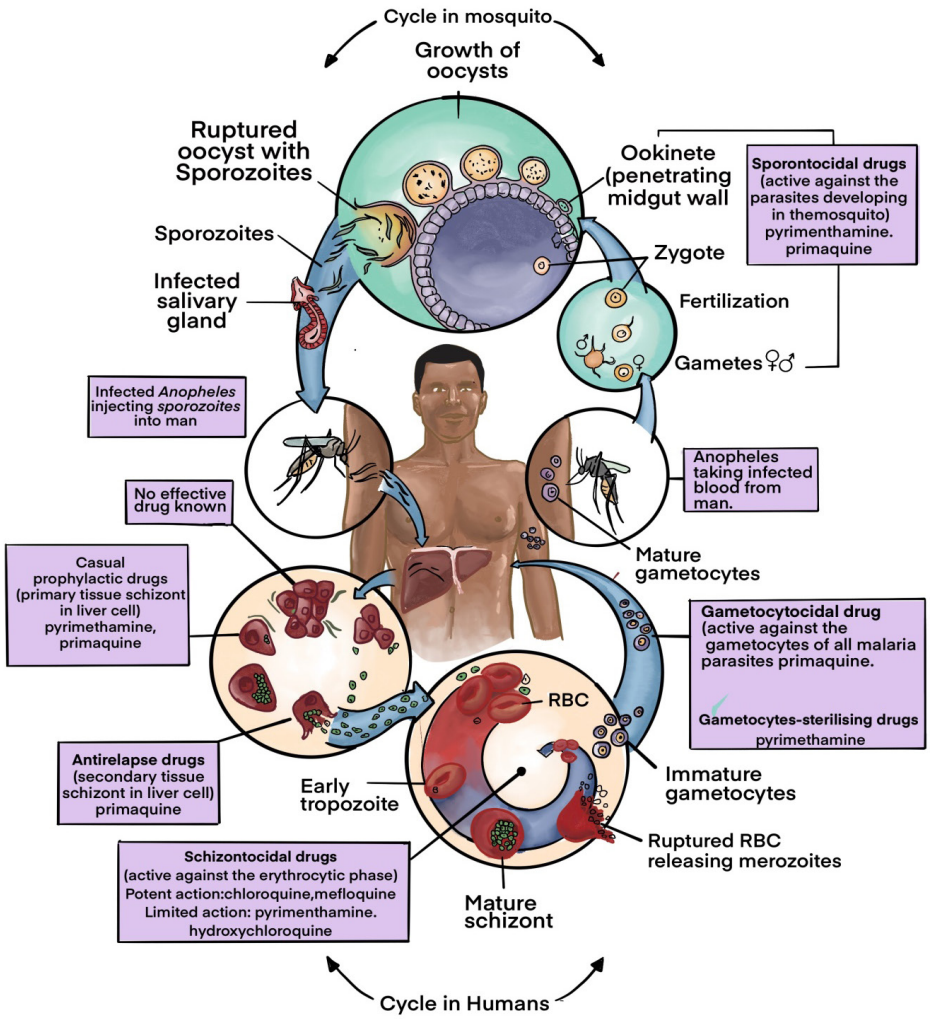


Figure 2: plasmodium's Life cycle and antimalarial medication

Self-assessment 3.3

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?

3.4. Antimalarial drugs prototypes

Learning Activity 3.4

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 39.20 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 300mg /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: 15mg/ 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: 15mg/kg body In adult: oral Quinine sulphate 10 mg / kg TID for 7 days
Severe malaria	Artesunate IV 2.4 mg/kg IV (time = 0), then at 12h and 24h, then once a day for three days. Then continue with artemether 20 mg 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 3.4

3) 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?
4) 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?
5) 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

3.5. Antimalarial drug dosage.

Learning Activity 3.5

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 dosage calculation.

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 q1Week, 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 4 hours, 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 3.5.1 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)

100mg 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 3.5.2 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 3.5

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.

3.6. Treatment of simple malaria

Learning Activity 3.6

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 3.6.1: 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 3.6.2: 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 3.6

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?

3.7. Treatment of severe malaria

Learning Activity 3.7

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 40mg/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 3.7

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?

3.8. Treatment of malaria for pregnant women

Learning Activity 3.8

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 visits

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 visits.

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.

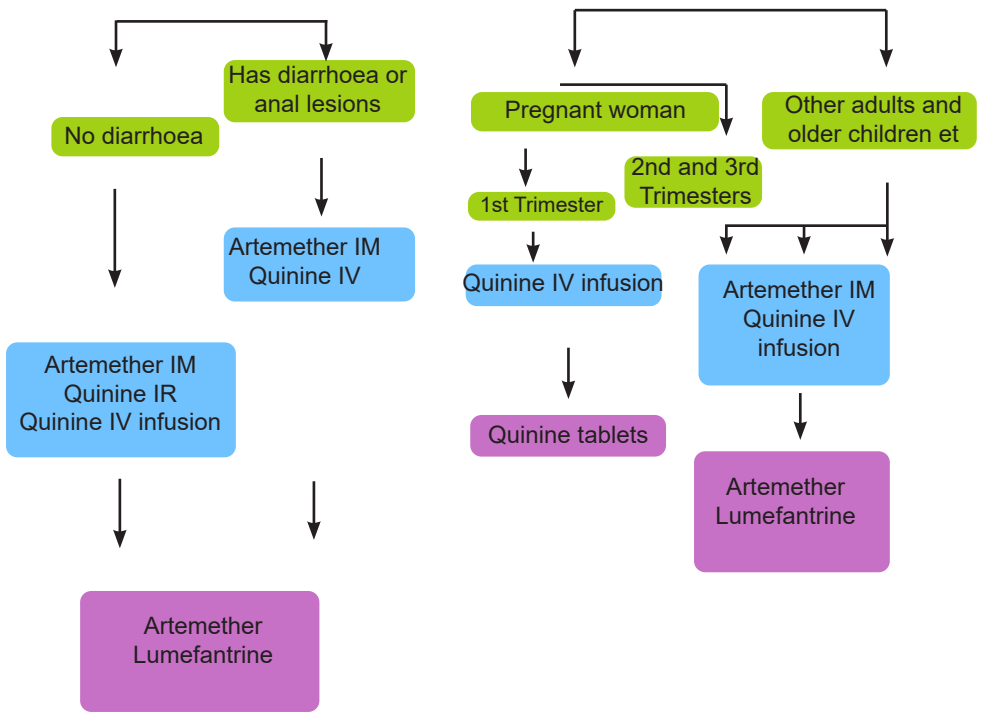
- In case of convulsions:
  - Administer diazepam, 10 mg IV slow; and if convulsions persist, administer diazepam, 10 mg in 500 ml of 5 % glucose to run slowly.
  - Treat or prevent hypoglycaemia;
  - Treat the fever if necessary;
  - Fill in the transfer card correctly and clearly,
  - Record all the 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 (APO) 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 3.8

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.

3.9. Non-malarial antiprotozoal medications (miscellaneous antiprotozoals)

Learning Activity 3.9

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 3.9

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

3.10. Health Education about Malaria and Amebiasis Treatment

Learning Activity 3.10

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 3.10

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?

3.11. End unit assessment

End of unit assessment

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

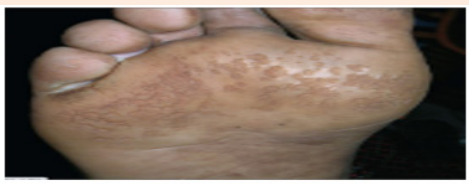
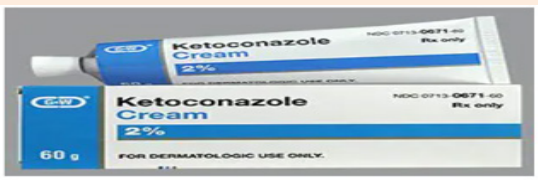
UNIT 4 : ANTIFUNGAL DRUGS

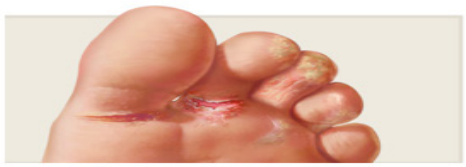
Key Unit Competence:

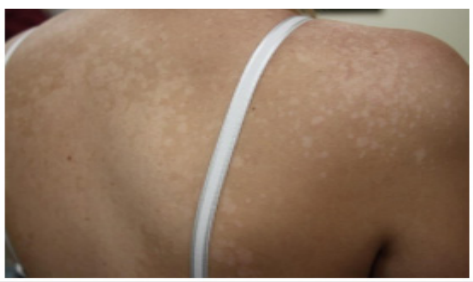
Utilize appropriately antifungal medications to manage different health condition at the primary healthcare settings

Introductory activity 4.0

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




1) Have you ever seen some of the medical conditions above?
2) Which types of medications have you seen being used for these medical conditions above?
3) Have you ever seen these medications in the images above?

4.1 Definition and classification of antifungal drugs

Learning Activity 4.1

Read the scenario below:

A 35-year-old male patient is on drugs that she applies as a cream between her toes. The only explanations she got from the prescribers is to apply the cream as prescribed and dry the area before application of the drug. She has limited information regarding the intent of the drug, and what she only knows is that the drug was prescribed for an infectious disease. She then doubts whether she is taking an antibiotic or antifungal or any other drug. She wants you to provide detailed information. Answer the following questions to provide explanations to him:

a) Explain what an antifungal drug is.

b) What are different classes of antifungal drugs according to where they exert their effects?

CONTENT SUMMARY

Fungal infections in humans range from conditions such as the annoying “athlete’s foot” to potentially fatal systemic infections. An infection caused by a fungus is called a mycosis. Fungi differ from bacteria in that the fungus has a rigid cell wall that is made up of chitin and various polysaccharides and a cell membrane that contains ergosterol. The composition of the protective layers of the fungal cell makes the organism resistant to antibiotics. Conversely, because of their cellular makeup, bacteria are resistant to antifungal drugs.

The incidence of fungal infections has increased with the rising number of immunocompromised individuals-patients with acquired immune deficiency syndrome (AIDS) and AIDS-related complex, those taking immunosuppressant drugs, those who have undergone transplantation surgery or cancer treatment, and members of the increasingly large elderly population, whose body is no longer able to protect itself from the many fungi that are found throughout the environment. For example, Candida, a fungus that is normally found on mucous membranes, can cause yeast infections or “thrush” in the gastrointestinal (GI) tract and yeast infections or “vaginitis” in the vagina.

Continued advancement of medical science offers life-saving treatment options for a variety of hematologic, oncologic, and rheumatologic conditions. Immunosuppression, a common therapeutic side-effect, predisposes patients to invasive fungal infections, which are escalating in prevalence. The development of effective, well tolerated antifungals has lagged behind the advances of antibacterial

therapy. Amphotericin B deoxycholate, an antifungal developed in the 1950s, marked a major therapeutic advance. Although very effective for the treatment of numerous invasive fungal infections, it is not without cost, and its side-effects often limit its use.

Antifungal drug can simply be defined as a drug used to treat fungal infections.

An antifungal agent is a drug that selectively eliminates fungal pathogens from a host with minimal toxicity to the host.

Antifungal agents are classified according to either their mechanism of action/ structure or where they exert their effect.

According to where they exert their effects, the antifungal drugs may be classified as systemic antifungals or topical antifungals

Most antifungal drugs interfere with biosynthesis or integrity of ergosterol, the major sterol in the fungal cell membrane. Others cause disruption of the fungal cell wall.

According to their mechanism of action or structure, antifungals are categorized in 4 main classes. These are azole antifungal drugs, polyene antifungal drugs, allylamine and morpholine antifungal drugs, and echinocandin antifungal drugs.

The azoles are a large group of antifungals used to treat systemic and topical fungal infections. The azoles include fluconazole, itraconazole, ketoconazole (Nizoral), posaconazole, and voriconazole. Although azoles are considered less toxic than some other antifungals, such as amphotericin B, they may also be less effective in very severe and progressive infections.

The polyene antifungal drugs include amphotericin, nystatin, and pimaricin. They interact with sterols in the cell membrane (ergosterol in fungi, cholesterol in humans) to form channels through which small molecules leak from the inside of the fungal cell to the outside.

Allylamines (naftifine, terbinafine) inhibit ergosterol biosynthesis at the level of squalene epoxidase. The morpholine drug, amorolfine, inhibits the same pathway at a later step.

The echinocandin antifungals are another group of antifungals. Drugs in this class include anidulafungin, caspofungin, and micafungin.

Self-assessment 4.1

3) You have a colleague of class in the associate nursing program who tells you that she has an onychomycosis (fungal infection of the nails). She has been prescribed an antifungal drug, and the prescribing person told her that there are 4 main classes of antifungal drugs according to their structure/mechanism of action, with specifications that the drug prescribed belongs to one of the classes. However, she does not remember these classes of antifungal drugs, and needs your assistance to remind her. Which classes of antifungal drugs will you tell your colleague?

4) A patient with a fungal infection asks the nurse why she cannot take antibiotics. The nurse explains that the reason for this is that a fungus is resistant to antibiotics because:

a) A fungal cell wall has fewer but more selective protective layers.

b) The composition of the fungal cell wall is highly rigid and protective.

c) A fungus does not reproduce by the usual methods of cell division.

d) Antibiotics are developed to affect only bacterial cell walls.

4.2 Antifungal drugs available at the primary health care settings

4.2.1 Systemic antifungals: azole and echinocandin antifungals

Learning Activity 4.2.1

5) Read carefully the scenario below:

A 50-year-old female patient is admitted at the healthcare facility with features of a fungal infection. The thorough assessment reveals that the patient has an infection that can be treated by antifungals for systemic use. You decide to avoid using an antifungal for topical use because you think it cannot work appropriately for this specific patient. Read the pharmacology book on systemic antifungals, with focus on focus on azoles and echinocandin antifungals and come up with at least 5 examples of antifungals for systemic use, belonging to these categories.

Guidance: Read the book of pharmacology brought by the teacher in class, on topic of antifungal drugs (focus on azoles and echinocandin antifungals).

CONTENT SUMMARY

The drugs used to treat systemic fungal infections can be toxic to the host and are not to be used indiscriminately. It is important to get a culture of the fungus causing the infection to ensure that the right drug is being used so that the patient is not put at additional risk from the toxic adverse effects associated with these drugs.

I. AZOLE ANTIFUNGALS

The azoles are a large group of antifungals used to treat systemic and topical fungal infections. The azoles include fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole (Vfend). Although azoles are considered less toxic than some other antifungals, such as amphotericin B, they may also be less effective in very severe and progressive infections.

1) Therapeutic Actions and Indications

These drugs bind to sterols and can cause cell death (a fungicidal effect) or interfere with cell replication (a fungistatic effect), depending on the type of fungus being affected and the concentration of the drug. Ketoconazole, fluconazole, and itraconazole work by blocking the activity of a sterol in the fungal wall. In addition, they may block the activity of human steroids, including testosterone and cortisol.

Posaconazole is one of the newest antifungals. This drug and voriconazole inhibit the synthesis of ergosterol, which leads to the inability of the fungus to form a cell wall, which results in cell death.

Fluconazole is indicated in the treatment of candidiasis, cryptococcal meningitis, other systemic fungal infections; prophylaxis for reducing the incidence of candidiasis in bone marrow transplant recipients.

Its usual dosage is:

- Adults: 200–400 mg PO on day 1, followed by 100 mg/d PO; IV route can be used, but do not exceed 200 mg/h,
- Paediatric population: 3–6 mg/kg PO; do not exceed 12 mg/kg.

Ketoconazole (Nizoral) is indicated in the treatment of aspergillosis, leishmaniasis, cryptococcosis, blastomycosis, moniliasis, coccidioidomycosis, histoplasmosis, and mucormycosis; topical treatment of mycoses (cream), and to reduce the scaling of dandruff (shampoo).

Its usual dosage is:

- Adult: 200 mg/d PO, up to 400 mg/d PO in severe cases
- Paediatric population (≥2 y): 3.3–6.6 mg/kg/d PO

- Paediatric (<2 y): Safety has not been established.
- Topical: as a shampoo and topical agents

Other indications of the azoles for systemic use include treatment of blastomycosis, histoplasmosis, and aspergillosis; prophylaxis of invasive Aspergillus and Candida infections in adults and children >13 y who are immunosuppressed secondary to antineoplastic, chemotherapy, graft-vs.-host disease following transplants, or hematological malignancies.

2) Pharmacokinetics

Ketoconazole, itraconazole and posaconazole are administered orally. Ketoconazole is also available as a shampoo and a cream. Fluconazole and voriconazole are available in oral and intravenous (IV) preparations, making it possible to start the drug intravenously for a serious infection and then switch to an oral form when the patient's condition improves and he or she is able to take oral medications. Ketoconazole is absorbed rapidly from the GI tract, with peak levels occurring within 1 to 3 hours. It is extensively metabolized in the liver and excreted through the feces.

Fluconazole reaches peak levels within 1 to 2 hours after administration. Most of the drug is excreted unchanged in the urine, so extreme caution should be used in the presence of renal dysfunction. Itraconazole is slowly absorbed from the GI tract and is metabolized in the liver by the CYP450 system. It is excreted in the urine and feces. Posaconazole is given orally, has a rapid onset of action, and peaks within 3 to 5 hours. It is metabolized in the liver and excreted in the feces. Voriconazole reaches peak levels in 1 to 2 hours if given orally, and at the onset of the infusion if given IV. It is metabolized in the liver with a half-life of 24 hours and is excreted in the urine.

3) Contraindications and Cautions

Ketoconazole has been associated with severe hepatic toxicity and should be avoided in patients with hepatic dysfunction to prevent serious hepatic toxicity. In addition, ketoconazole is not the drug of choice for patients with endocrine or fertility problems because of its effects on these processes. Although fluconazole should be used with caution in the presence of liver or renal impairment, because it could cause liver or renal toxicity, fluconazole is not associated with the endocrine problems seen with ketoconazole.

Because itraconazole has been associated with hepatic failure, should not be used in patients with hepatic failure, and should be used with caution in those with hepatic impairment. It is not known whether posaconazole crosses the placenta or enters breast milk, so it should not be used during pregnancy or lactation unless the benefi ts clearly outweigh the potential risks. Caution should be used if posaconazole is

used in the presence of liver impairment because it can cause liver toxicity. Carefully monitor patients for bone marrow suppression and GI and liver toxicity if using this drug.

Voriconazole should not be used with any other drugs that prolong the QTc interval because that could be worsened and can cause ergotism if taken with ergot alkaloid; so it should not be combined with ergots.

4) Adverse Effects

Many of the azoles are associated with liver toxicity and can cause severe effects on a fetus or a nursing baby.

5) Clinically Important Drug–Drug Interactions

Ketoconazole and fluconazole strongly inhibit the CYP450 enzyme system in the liver and are associated with many drug–drug interactions, such as increased serum levels of the following agents: cyclosporine, digoxin, oral hypoglycemics, warfarin, oral anticoagulants, and phenytoin. If these combinations cannot be avoided, closely monitor patients and anticipate the need for dose adjustments. A drug guide should be consulted any time one of these drugs is added to or removed from a drug regimen. Itraconazole has a black box warning regarding the potential for serious cardiovascular effects if it is given with lovastatin, simvastatin, triazolam, midazolam, pimozide, or dofetilide. These combinations should be avoided. Voriconazole and posaconazole should not be used with any other drugs that prolong the QTc interval and can cause ergotism if taken with ergot alkaloids.

II. ECHINOCANDIN ANTIFUNGALS

The echinocandin antifungals are another group of antifungals. Drugs in this class include anidulafungin, caspofungin, and micafungin.

1) Therapeutic Actions and Indications

The echinocandins work by inhibiting glucan synthesis. Glucan is an enzyme that is present in the fungal cell well but not in human cell walls. If this enzyme is inhibited, the fungal cell wall cannot form, leading to death of the cell wall.

The echinocandins are mainly used in the treatment of candidemia (infection of the blood stream) and other forms of Candida infection, intraabdominal infections, and esophageal candidiasis.

They are also used in the treatment of invasive aspergillosis in patients who do not respond or are intolerant to other therapies.

Finally, they can be used in the treatment of patients with esophageal candidiasis; prophylaxis of Candida infections in patients with hematopoietic stem cell transplant.

The usual dosage of anidulafungin is 100–200 mg IV on day 1, then 50–100 mg/d IV for 14 d; with the dose varying with infection being treated.

2) Pharmacokinetics

Anidulafungin is given as a daily IV infusion for at least 14 days. It has a rapid onset of action, is metabolized by degradation, and has half-life of 40 to 50 hours. This drug is excreted in the feces. Caspofungin is available for IV use. This drug is slowly metabolized in the liver, with half-lives of 9 to 11 hours, then 6 to 48 hours, and then 40 to 50 hours. It is bound to protein and widely distributed throughout the body. It is excreted through the urine. Micafungin is an IV drug. It has a rapid onset, a half-life of 14 to 17 hours, and is excreted in the urine.

3) Contraindications and Cautions

Anidulafungin may cross the placenta and enter breast milk and should not be used by pregnant or lactating women. Caution must be used in the presence of hepatic impairment because it can be toxic to the liver. Caspofungin can be toxic to the liver; therefore, reduced doses must be used if a patient has known hepatic impairment. Caspofungin is embryotoxic in animal studies and is known to enter breast milk; therefore, it should be used with great caution during pregnancy and lactation. Because of the potential for adverse reactions in the fetus or the neonate, micafungin should be used during pregnancy and lactation only if the benefits clearly outweigh the risks.

4) Adverse Effects

Anidulafungin and caspofungin are associated with hepatic toxicity, and liver function should be monitored closely when using these drugs. Potentially serious hypersensitivity reactions have occurred with micafungin. In addition, bone marrow suppression can occur; monitor patients closely.

5) Clinically Important Drug-Drug Interactions

Concurrent use of cyclosporine with caspofungin is contraindicated unless the benefit clearly outweighs the risk of hepatic injury.

Self-assessment 4.2.1

6) The antifungal drugs for systemic use are more likely to be less toxic compared to the antifungal drugs for topical use. TRUE or FALSE

7) Ketoconazole is an echinocandin antifungal for systemic use. TRUE or FALSE

8) Anidulafungin and caspofungin are associated with hepatic toxicity, and liver function should be monitored closely when using these drugs.

4.2.2 Systemic antifungals: other antifungal agents

Learning Activity 4.2.2

Read carefully the scenario below:

A 5-year-old male patient consults the healthcare facility where you are carrying out the clinical practice. He has mouth and tongue ulcerations following long-term use of cephalosporins of third generation. You decide that the patient has a fungal condition that requires to be treated with an antifungal known as "nystatin". You then decide to prescribe that antifungal agent.

i) What are the main indications of nystatin?

j) What is the usual dosage of nystatin?

Guidance: Read the book of pharmacology brought by the teacher in class, on topic of antifungal drugs.

CONTENT SUMMARY

Other antifungal drugs that are available do not fit into either of these classes. These include amphotericin B, flucytosine, griseofulvin, and nystatin.

1) Therapeutic Actions and Indications

Other antifungal agents work to cause fungal cell death or to prevent fungal cell reproduction. **Amphotericin B** is a very potent drug with many unpleasant adverse effects. The drug binds to the sterols in the fungus cell wall, changing cell wall permeability. This change can lead to cell death (fungicidal effect) or prevent the fungal cells from reproducing (fungistatic effect). Because of the many adverse effects associated with this agent, its use is reserved for progressive, potentially fatal infections.

Amphotericin B is mainly used in the treatment of aspergillosis, leishmaniasis, cryptococcosis, blastomycosis, moniliasis, coccidioidomycosis, histoplasmosis and mucormycosis; use is reserved for progressive, potential fatal infections due to many associated adverse effects.

The usual dosage for amphotericin B is 0.25–1.5 mg/kg/d IV based on the infection being treated.

Flucytosine is a less toxic drug that alters the cell membrane of susceptible fungi, causing cell death. The uses of flucytosine are limited to the treatment of systemic infections caused by Candida or Cryptococcus. Its usual dosage is 50–150 mg/kg/d PO in divided doses at 6-h intervals.

Griseofulvin is an older antifungal that acts in much the same way, changing cell membrane permeability and causing cell death. Griseofulvin is usually indicated in the treatment of variety of ringworm or tinea infections caused by susceptible Trichophyton species, including tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis, and tinea unguium.

The dosage of griseofulvin is as follows:

Tinea corporis, tinea cruris, and tinea capitis:

Adult: 500 mg (microsize) or 330–375 mg/d (ultramicrosize) PO

Tinea pedis and tinea unguium:

Adult: 0.75–1 g (microsize) or 660–750 mg (ultramicrosize) PO daily

Paediatric population: (>2 y): 11 mg/kg/d (microsize) or 7.3 mg (ultramicrosize) PO daily (not recommended for children ≤2 y)

Nystatin binds to sterols in the cell wall, changing membrane permeability and allowing leaking of the cellular components, which will result in cell death. Nystatin is usually indicated in the treatment of candidiasis (oral form); treatment of local candidiasis, vaginal candidiasis, and cutaneous and mucocutaneous infections caused by Candida species.

Its usual dosage is 500,000–1,000,000 units t.i.d. PO; continue for 48 h after resolution to prevent relapse; also used topically.

1) Pharmacokinetics

Amphotericin B and flucytosine are available in IV form. They are excreted in the urine, with an initial half-life of 24 hours and then a 15-day half-life. Their metabolism is not fully understood. Flucytosine is well absorbed from the GI tract, with peak levels occurring in 2 hours. Most of the drug is excreted unchanged in the urine and a small amount in the feces, with a half-life of 2.4 to 4.8 hours. Griseofulvin is administered orally and reaches peak levels in around 4 hours. It is metabolized in the liver and excreted in the urine with a half-life of 24 hours. Nystatin is not absorbed from the GI tract and passes unchanged in the stool.

2) Contraindications and Cautions

Amphotericin B has been used successfully during pregnancy, but it should be used cautiously. It crosses into breast milk and should not be used during lactation because of the potential risk to the neonate. Because flucytosine is excreted primarily in the urine, extreme caution is needed in the presence of renal impairment because drug accumulation and toxicity can occur. Toxicity is associated with serum levels higher than 100 mcg/mL. Because of the potential for adverse reactions in the fetus or neonate, flucytosine should be used during pregnancy and lactation only

if the benefits clearly outweigh the risks. It is not known whether nystatin crosses the placenta or enters breast milk, so it should not be used during pregnancy or lactation unless the benefits clearly outweigh the potential risks.

3) Adverse Effects

Adverse effects of these drugs are related to their toxic effects on the liver and kidneys. Patients should be monitored closely for any changes in liver or kidney functions. Bone marrow suppression has also been reported with the use of these drugs. Rash and dermatological changes have been reported with these antifungals. Amphotericin B is associated with severe renal impairment, bone marrow suppression, GI irritation with nausea, vomiting, and potentially severe diarrhea, anorexia and weight loss, and pain at the injection site with the possibility of phlebitis or thrombophlebitis. Adverse effects of griseofulvin are relatively mild, with headache and central nervous system (CNS) changes occurring most frequently.

4) Clinically Important Drug-Drug Interactions

Patients who receive amphotericin B should not take other nephrotoxic drugs such as nephrotoxic antibiotics or antineoplastics, cyclosporine, or corticosteroids unless absolutely necessary because of the increased risk of severe renal toxicity.

Self-assessment 4.2.2

A 55-year-old male patient is being treated for cryptococcal meningitis following his immunosuppression with AIDS. The treating team decides to prescribe amphotericin B because they judge it may be beneficial for this patient.

a) What are other indications of amphotericin B?

b) What are the adverse effects of amphotericin B?

4.2.3 Topical antifungal agents

Learning Activity 4.2.3

A 20-year-old female patient consults the healthcare facility where you are carrying out your clinical practice as an associate nurse student. The patient complains of ulcerations between toes, itching and pain. He reports that she does not usually taker care of her toes properly, and most of the time she does not dry her feet adequately after bath, as she rushes for work early morning.

On your physical examination, you realize that the patient has athlete's foot, and you decide to prescribe a topical antifungal agent.

c) Give any three examples of topical azole-type antifungals

d) What are the nursing considerations would you take into account while prescribing topical antifungals?

Guidance: Use the book of pharmacology brought by the teacher in class, and read on topic of antifungals, subtopic of topical antifungals

CONTENT SUMMARY

Some antifungal drugs are available only in topical forms for treating a variety of mycoses of the skin and mucous membranes. Some of the systemic antifungals are also available in topical forms. Fungi that cause these mycoses are called dermatophytes. These diseases include a variety of tinea infections, which are often referred to as ringworm, although the causal organism is a fungus, not a worm.

These mycoses include tinea infections such as athlete's foot (tinea pedis), jock itch (tinea cruris), and yeast infections of the mouth and vagina often caused by Candida. Because the antifungal drugs reserved for use as topical agents are often too toxic for systemic administration, care is necessary when using them near open or draining wounds that might permit systemic absorption.

Topical antifungals include the azole-type antifungals such as butoconazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole nitrate, sulconazole, terconazole, and tioconazole. Topical antifungals also include other antifungals such as butenafine, ciclopirox, gentian violet, naftifine, tolnaftate, and undecylenic acid.

1) Therapeutic Actions and Indications

The topical antifungal drugs work to alter the cell permeability of the fungus, causing prevention of replication and fungal death. They are indicated only for local treatment of mycoses, including tinea infections.

Butoconazole is available as vaginal cream; applied only once a day for 4 wk. It is available over the counter (OTC) for treatment of vaginal Candida infections.

Clotrimazole is available OTC as a cream, lotion, or solution; applied as a thin layer twice a day for 2–4 wk. It is used in the treatment of oral and vaginal Candida infections; tinea infections.

Ketoconazole is available in cream, gel, foam, and shampoo form; applied once to twice daily for 2–4 wk. It is used in the treatment of seborrheic dermatitis, tinea corporis, tinea cruris, tinea pedis.

Miconazole is available as an OTC product in several topical forms (vaginal suppository, cream, powder, solution, ointment, gel and spray); applied twice daily for 2–4 wk. It is used in the treatment of local, topical mycoses, including bladder and vaginal infections and athlete's foot.

Terbinafine is available as a cream or gel; used for 1–4 wk; applied twice daily. It is used in the short-term (1–4 wk) treatment of topical mycosis; treatment of tinea infections.

Gentian violet is available as a topical solution; applied twice a day to affected area. It is used in the treatment of topical mycosis.

Naftifine is available as a cream or gel; applied twice a day for up to 4 wk. hort-term treatment of severe topical mycosis (up to 4 wk). It is used in the short-term treatment of severe topical mycosis (up to 4 wk).

2) Pharmacokinetics

These drugs are not absorbed systemically and do not undergo metabolism or excretion in the body.

3) Contraindications and Cautions

Because these drugs are not absorbed systemically, contraindications are limited to a known allergy to any of these drugs and open lesions. Econazole can cause intense, local burning and irritation and should be discontinued if these conditions become severe. Gentian violet stains skin and clothing bright purple; in addition, it is very toxic when absorbed, so it cannot be used near active lesions. Naftifine, oxiconazole, and sertaconazole nitrate should not be used for longer than 4 weeks due to the risk of adverse effects and possible emergence of resistant strains of fungi. Sulconazole should not be used for longer than 6 weeks due to the risk of adverse effects and possible emergence of resistant strains of fungi. Terbinafine should not be used for longer than 4 weeks. This drug should be stopped when the fungal condition appears to be improved or if local irritation and pain become too great to avoid toxic effects.

4) Adverse Effects

When these drugs are applied locally as a cream, lotion, or spray, local effects include irritation, burning, rash, and swelling. When they are taken as a suppository or troche, adverse effects include nausea, vomiting, and hepatic dysfunction (related to absorption of some of the drug by the GI tract) or urinary frequency, burning, and change in sexual activity (related to local absorption in the vagina).

Self-assessment 4.2.3

After going through the session of topical antifungals, answer the following questions:

1) What are the adverse effects of topical antifungals used as suppositories?
2) Give the indications of topical clotrimazole.

4.3 End unit assessment

End of unit assessment

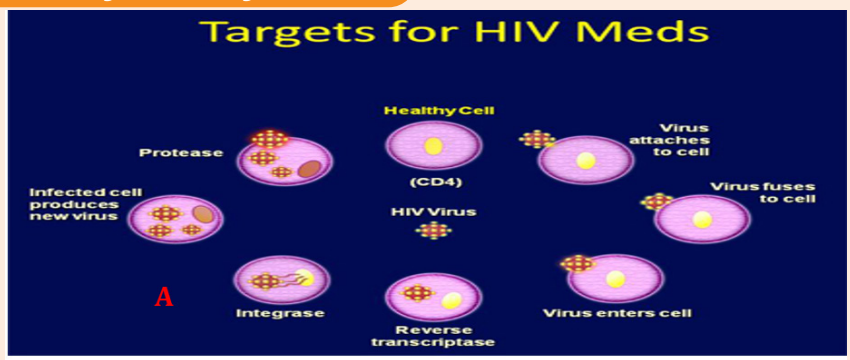
1) The order reads, “Give nystatin (Mycostatin) suspension, 500,000 units by mouth (swish and swallow) 4 times a day for 1 week.” The medication is available in a suspension of 100,000 units per mL. How many milliliters will the nurse give per dose?
2) The nurse notes in a patient’s medication history that the patient is taking terbinafine (Lamisil). Based on this finding, the nurse interprets that the patient has which disorder?
   a) Vaginal candidiasis
   b) Cryptococcal meningitis
   c) Invasive aspergillosis
   d) Fungal infection of toenails or fingernails
3) What are the adverse effects of topical antifungal agents?
4) Terbinafine cream should be used in the long-term (at least 10 weeks) treatment of topical mycosis in order to get the result. TRUE or FALSE
5) Antifungals in topical forms are used to treat a variety of systemic mycoses of the internal body organs. TRUE or FALSE

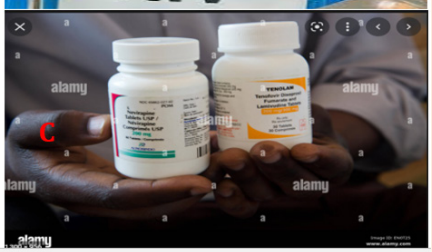
UNIT 5: ANTIVIRAL DRUGS

Key Unit Competence:

Utilize antiretroviral medications to limit HIV/AIDS transmission

Introductory activity 5.0





Observe the images (A, B, C) above and describe briefly what they indicate for you.

5.1. Introduction to antiretroviral drugs

Learning Activity 5.1

During your clinical practice ,you receive a client in consultation. In data collection, the client reports that he is taking antiretroviral drug.

1) What is an antiretroviral drug?
2) What is a protease inhibitor?

Guidance: Use internet and library textboks.

CONTENT SUMMARY

Antiviral: An agent that kills a virus or that suppresses its ability to replicate and, hence, inhibits its capability to multiply and reproduce.

For example, amantadine (Symmetrel) is a synthetic antiviral. It acts by inhibiting the multiplication of the influenza A virus. It was used to lessen the severity of the disease, particularly in individuals at high-risk such as those who are immunosuppressed or in a nursing home.

The antivirals that have been developed are generally less effective than one would like. Viruses can replicate rapidly and, in many cases sloppily, giving rise to mutations that make them resistant to drugs. And for fast-moving viral infections like flu or a cold, a drug must be very powerful to make a difference before the disease runs its natural course.

Antivirals and Antiretrovirals are a class of medication specifically used to treat viral and retroviral infections caused by viruses like HIV, herpes viruses, hepatitis B and C. Antivirals are a class of drugs which are used to treat viral infections. The antiviral drugs target diverse group of viruses such as herpes, hepatitis, and influenza viruses. Whereas antiretroviral drugs are the drugs that are used to fight retrovirus infections which mainly include HIV. Different classes of antiretroviral drugs act on different stages of the HIV life cycle.

Retrovirus is a group of viruses that belong to the family Retroviridae and that characteristically carry their genetic blueprint in the form of ribonucleic acid (RNA). Retroviruses are named for an enzyme known as reverse transcriptase, which was discovered independently in 1971 by American virologists Howard Temin and David Baltimore. Reverse transcriptase transcribes RNA into deoxyribonucleic acid (DNA), a process that constitutes a reversal of the usual direction of cellular transcription (DNA into RNA). The action of reverse transcriptase makes it possible for genetic material from a retrovirus to become permanently incorporated into the DNA genome of an infected cell; the enzyme is widely used in the biological sciences to synthesize genes.

Integrase inhibitor: a drug that inhibits the activity of the virus-specific enzyme integrase, an encoded enzyme needed for viral replication; blocking this enzyme prevents the formation of the HIV-1 provirus.

Interferon: tissue hormone that is released in response to viral invasion; blocks viral replication nonnucleoside reverse transcriptase inhibitors: drugs that bind to sites on the reverse transcriptase within the cell cytoplasm, preventing RNA- and DNA-dependent DNA polymerase activities needed to carry out viral DNA synthesis; prevents the transfer of information that allows the virus to replicate and survive.

Nucleoside reverse transcriptase inhibitors: drugs that prevent the growth of the viral DNA chain, preventing it from inserting into the host DNA, so viral replication cannot occur.

Protease inhibitors: drugs that block the activity of the enzyme protease in HIV; protease is essential for the maturation of infectious virus, and its absence leads to the formation of an immature and noninfective HIV particle.

CCR5 coreceptor antagonist: a drug that blocks the receptor site on the T cell membrane that the HIV virus needs to interact with in order to enter the cell.

Fusion inhibitor: a drug that prevents the fusion of the HIV-1 virus with the human cellular membrane, preventing it from entering the cell.

Self-assessment 5.1

1) which of the following is a definition of antiviral drugs?

   a) Antivirals are a class of drugs which are used to treat viral infections

   b) Antivirals are a class of drugs which are used to treat viral and bacterial infections

   c) Antivirals are a class of drugs which are used to treat retroviral infections

   d) Antivirals are a class of drugs which are used to treat viral and retroviral infections

2) You receive a client with signs and symptoms of helps simplex. Among the two following groups of drugs, which one will you choose as effective to the disease?

   a) Antiretroviral drugs

   b) Antiviral drugs

3) With an example of the virus infections. Differentiate antiviral and retroviral drugs

5.2. Classification of antiretroviral drugs

Learning Activity 5.2

You are an asociate nurse carrying out the clinical placement. You receive a patient at the health facility who has been diagnosed with HIV/AIDS. What does an associate nurse will tell the patient?

1) Which classes of antiretroviral drugs can be used in HIV/AIDS management?

2) What are the five basic goals of ART?

CONTENT SUMMARY

In this lesson we discuss on classification of antiretroviral drugs. HIV infection has been transformed from a near-certain death sentence to a manageable chronic disease. Because of viruses are contained inside human cells while they are in the body, researchers have difficulty developing effective drugs that destroy a virus without harming the human host. Since the introduction of ART, the incidence of new opportunistic infections has declined dramatically. For example, the incidences of cytomegalovirus retinitis and disseminated mycobacterial infection have fallen by as much as 75% to 80%. In many patients with low CD4 T-cell counts, ART has caused CD4 counts to rise, restoring some immunocompetence and permitting withdrawal of prophylactic drugs.

Patients with HIV infection should receive ART regardless of the CD4 count or phase of HIV disease. Treatment has five basic goals: Maximal and long-lasting suppression of viral load, restoration and preservation of immune function, improved quality of life, reduction of HIV-related morbidity and mortality and prevention of HIV transmission. Most patients take several antiretroviral drugs typically two nucleoside reverse transcriptase inhibitors (NRTIs) combined with either a PI or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

These highly effective regimens can reduce plasma HIV to undetectable levels, causing CD4 T-cell counts to return toward normal, thereby restoring some immune function. However, despite these advances, treatment cannot cure HIV. The HIV mutates over time, presenting a slightly different configuration with each new generation. Treatment of AIDS and ARC has been difficult for two reasons: (1) the length of time the virus can remain dormant within the T cells (i.e., months to years), and (2) the adverse effects of many potent drugs, which may include further depression of the immune system. A combination of several different antiviral drugs is used to attack the virus at various points in its life cycle to achieve maximum effectiveness with the least amount of toxicity.

Antiretroviral drugs are classified into six classes of antiretroviral drugs. Four classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and protease inhibitors (PIs) inhibit HIV enzymes.

The other two classes: HIV fusion inhibitors and CCR5 antagonists, work outside CD4 cells to block HIV entry.

NRTIs suppress HIV replication in two ways: (1) they become incorporated into the growing strand of viral DNA (through the actions of reverse transcriptase) and thereby prevent further strand growth, and (2) they compete with natural nucleoside triphosphates for binding to the active center of reverse transcriptase and thereby competitively inhibit the enzyme. To interact with reverse transcriptase, NRTIs must first undergo intracellular conversion to their active (triphosphate) forms.

The NNRTIs differ from the NRTIs in structure and mechanism of action. As their name suggests, the NNRTIs have no structural relationship with naturally occurring nucleosides. Also unlike NRTIs, the NNRTIs are active only against HIV-1. In practice, they are usually combined with an NRTI. The NNRTIs bind to the active center of reverse transcriptase enzyme. At this location, the NNRTI causes stereochemical changes (i.e., changes in the spatial arrangement of atoms forming the structure of molecules). This hampers the ability of nucleosides to bind, which inhibits DNA replication and promotes premature termination of the growing DNA strand.

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

The NRTIs were the first drugs used against HIV infection. As their name suggests, the NRTIs are chemical relatives of naturally occurring nucleosides or nucleotides, the building blocks of DNA. At this time, seven NRTIs are available: Abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine. The NRTIs are effective against both HIV-1 and HIV-2; however, their activity is greater for HIV-1. The NRTIs are ineffective as monotherapy because resistance develops rapidly. First-line antiretroviral regimens include two NRTIs and one other drug. The availability of combination antiretroviral products has simplified treatment.

Mechanism of Action

All NRTIs are prodrugs that inhibit HIV replication by suppressing synthesis of viral DNA. To do this, they must first undergo intracellular conversion to their active (phosphate) form. In their active form, they act as substrates for reverse transcriptase. However, after they become incorporated into the growing DNA strand, they prevent reverse transcriptase from adding more bases. As a result, all further growth of the DNA strand is blocked. In addition to causing premature strand termination, the activated NRTI competes with natural nucleoside triphosphates for binding to the active site of reverse transcriptase.

Adverse Effects

The NRTIs share a core of adverse effects associated with mitochondrial toxicity. Recall that mitochondria are cellular organelles that take in nutrients and convert them into ATP for energy. NRTIs can disrupt synthesis of mitochondrial DNA and can thereby impair mitochondrial function.

The main adverse effects of NRTIs are: Lactic acidosis, hepatic steatosis. Other adverse effects include: pancreatitis and myopathies, which are likely tied to lactic acidosis. Adverse effects of individual NRTIs are discussed separately.

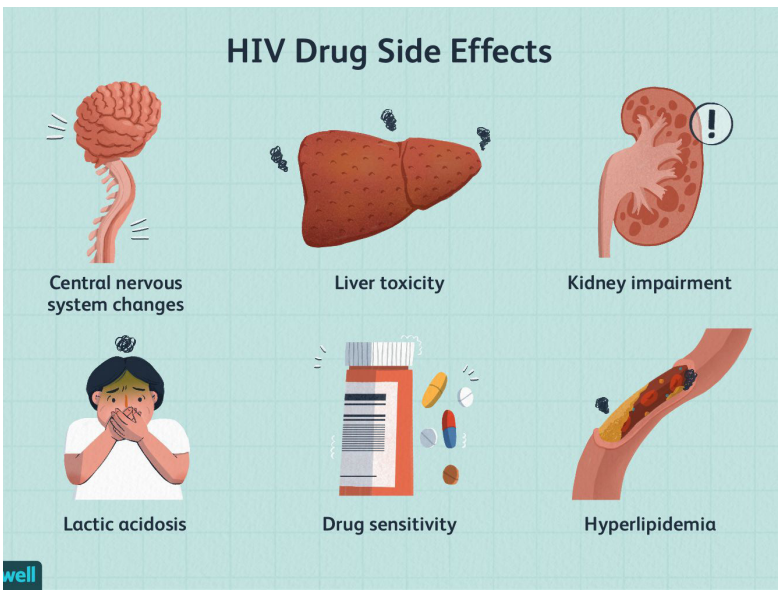
Drug Interactions

NRTIs have fewer drug interactions than most antiretroviral drugs, in part because most are not metabolized by the P450 enzymes. Interactions of individual drugs are discussed separately.

Table 5.1.1: NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

Drug name	Dosage/route	Usual indications
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Abacavir (ziagen)	Adult: 300mg PO b.i.d or 600mg/d PO Pediatric: 8mg/kg PO b.i.d or 16mg/kg PO once a day	combination therapy for the treatment of adults and children with HIV
Didanosine (videx)	Adult: 250-400mg/d PO or 125-250 mg PO b.i.d Pediatric: 100-120 mg/ m^2PO b.i.d	Treatment of advanced infections in adults and children with HIV as part of combination therapy
Emtricitabine (emtriva)	Adult: 200mg/d PO or 240mg oral solution/d Pediatric (3mo to 17 years): 6mg/kg/d PO to a maximum 240mg	Part of combination therapy for treatment of HIV-1 infection
Lamivudine (epivir)	Adult:150mg PO b.i.d or 300mg/d PO; for chronic hepatitis B , 100mg PO qd Pediatric (3 mo to 16 years): 4 mg/kg PO b.i.d	With other antiretroviral agents for the treatment of adults and children with HIV; as an oral solution for the treatment of chronic hepatitis B
Stavudine (zerit)	Adult, child (≥60 kg): 40mg PO q 12h Adult, child (30-60kg): 30mg PO q12h Pediatric: other doses based on weight	Treatment of patients with HIV in combination with other antiretroviral agents

Tenofovir (viread)	Adult: 300mg/d PO Pediatric (2-11 year): 8mg/kg/d PO (for HIV not recommended for hepatitis B)	Treatment of adults/children with HIV infection in combination with other antiretroviral drugs; treatment of chronic hepatitis B
Zidovudine (retrovir)	Adult: 600mgmg/d PO divided Pediatric (6wk to 12 years): 600mg/d PO in 2 divided doses Maternal: 100mg PO five per day from 14 weeks gestation until start of labor	Treatment of symptomatic HIV in adults and children as part of combination therapy; prevention of maternal transmission of HIV



NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The NNRTIs differ from the NRTIs in structure and mechanism of action. As their name suggests, the NNRTIs have no structural relationship with naturally occurring nucleosides. Also unlike NRTIs, the NNRTIs are active only against HIV-1. In practice, they are usually combined with an NRTI. At this time, five NNRTIs are available: efavirenz (Sustiva), nevirapine (Viramune), Delavirdine (Rescriptor), etravirine (Intelence), and rilpivirine (Edurant).

Mechanism of Action

In contrast to the NRTIs, the NNRTIs bind to the active center of reverse transcriptase enzyme. At this location, the NNRTI causes stereochemical changes (i.e., changes in the spatial arrangement of atoms forming the structure of molecules). This hampers the ability of nucleosides to bind, which inhibits DNA replication and promotes premature termination of the growing DNA strand.

Adverse Effects

Unlike NRTIs, there are no adverse effects shared by all NNRTIs. However, two of the NNRTIs, efavirenz and rilpivirine, can both cause CNS effects.

Drug Interactions

The NNRTIs have multiple drug interactions with commonly used drugs across many drug classes. These vary according to the individual NNRTI in question.

Table 5.1.2: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Drug name	Dosage/route	Usual indications
Nonnucleoside reverse transcriptase inhibitors		
Delavirdine (Rescriptor)	Adult: 400mg PO t.i.d	Part of combination therapy regimens for treatment of HIV in adults
Efavirenz (Sustiva)	Adult:600mg/d PO Pediatric: dose determined by age and weight	Treatment of adults and children with HIV in combination with other antiretroviral agents
Etravirine (Intelence)	Adult: 200mgPO b.i.d after a meal Pediatric: based on weight, 100-200mg PO b.i.d	Treatment of HIV in adults with treatment experience who have evidence of viral replication and HIV strains resistant to standard therapy
Nevirapine (Viramune)	Adult : 200mg/d PO for 14 d, then 200mg PO b.i.d Pediatric: 150mg/m^2PO for 14 d, then 150 mg/m^2PO for 14 d, then 150 mg/m^2PO b.i.d	Treatment of adults or children with HIV in combination with other antiretroviral agents
Rilpivirine (edurant)	Adult: 25mg/d PO with food	Combination treatment of adults with HIV-1 infection

PROTEASE INHIBITORS

PIs are active against both HIV-1 and HIV-2. They are among the most effective antiretroviral drugs available. When used in combination with NRTIs, they can reduce viral load to a level that is undetectable with current assays.

As with other antiretroviral drugs, HIV resistance can be a significant problem. Mutant strains of HIV that are resistant to one PI are likely to be cross-resistant to other PIs. In contrast, since PIs do not share the same mechanism as other antiretroviral drugs, cross-resistance between PIs and these drugs does not occur. To reduce the risk for resistance, PIs should never be used alone; rather, they should always be combined with at least one reverse transcriptase inhibitor, and preferably two.

Nine PIs are available: atazanavir, darunavir, fosamprenavir, indinavir, lopinavir (with ritonavir), nelfinavir, ritonavir, saquinavir, and tipranavir.

Mechanism of Action

Maturation is necessary for HIV to infect CD4 cells; immature forms are noninfectious. Protease inhibitors prevent HIV maturation by blocking the HIV enzyme protease. It may help to look at the process of HIV maturation.

When the various enzymes and structural proteins of HIV are synthesized, they are not produced as separate entities; rather, they are strung together in large polyproteins. Protease catalyzes the cleavage of bonds in the polyproteins, thereby freeing the individual enzymes and structural proteins. Once these components have been freed, HIV uses them to complete its maturation. Protease inhibitors bind to the active site of HIV protease and prevent the enzyme from cleaving HIV polyproteins. As a result, the structural proteins and enzymes of HIV are unable to function, and hence the virus remains immature and non-infectious.

Adverse Effects

There are several adverse effects that all protease inhibitors have in common. These include hyperglycemia and the development of diabetes, lipodystrophy (fat redistribution), elevation of serum transaminases, and decreased cardiac conduction velocity. They can also increase bleeding in patients with hemophilia.

Drug Interactions

All PIs are metabolized by cytochrome P450 enzymes, and all PIs can inhibit selected cytochrome P450 enzymes. Typically, they will also induce other enzymes. As a result, PIs can interact with drugs that inhibit or induce P450 enzymes and with drugs that are substrates for P450 enzymes. Not all interactions are harmful, of course. By inhibiting selected P450 enzymes one PI can increase the level of another PI and can thus intensify therapeutic effects. One PI—ritonavir [Norvir]—is routinely

combined with other PIs with the specific purpose of increasing the therapeutic effects of the other PI. In this technique, known as ritonavir boosting, the dose of ritonavir is low: 100 to 400 mg/day. This dosage is too low to contribute significant antiviral effects, but still high enough to inhibit P450 metabolism. Unfortunately, most interactions with PIs are not beneficial. We will highlight interactions commonly experienced by patients with HIV in our discussion of individual PIs.

Table 5.1.3: PROTEASE INHIBITORS

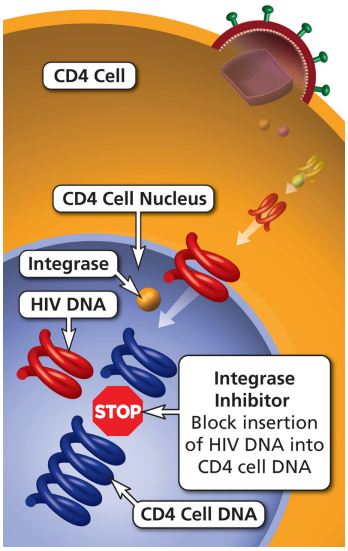
Drug name	Dosage/route	Usual indications
Protease inhibitors		
Atazanavir (reyataz)	Adult: 300mg/d PO with ritonavir Pediatric:150-300mg/d PO with ritonavir	Treatment of adults/ children with HIV as part of combination therapy
Darunavir (prezista)	Adult: 600mg/d PO b.i.d with ritonavir 100mg PO b.i.d Pediatric: dose based on weight and surface area	Treatment of adults/ children with advanced HIV disease with progression following standard treatment, used as part of combination therapy that must contain ritonavir
Fosamprenavir (lexiva)	Adult: 1400mg/PO b.i.d with 100mg/d ritonavir PO or 700mg PO b.i.d with ritonavir 100mg PO b.i.d Pediatric:18-30mg/kg b.i.d oral suspension, based on weight with ritonavir 3mg/kg PO b.i.d	part of combination therapy for the treatment of HIV
Indinavir (crixivan)	Adult: 800mg PO q8h; dosage adjusted based on other drugs used	Treatment of adults with HIV as part of combination therapy

Lopinavir/ ritonavir (kaletra)	Adult: dose varies based on indication and other antivirals: 400/100 mg-800/200mg qd or b.i.d PO Pediatric (14 d to 12 years): dose based on weight	Treatment of adults and children with HIV in combination with other antiretroviral agents
Nelfinavir (viracept)	Adult: 750mg PO t.id or 1250 mg PO b.i.d Pediatric (2-13 years): 45-55mg/kg PO b.i.d or 25-35 mg/kg PO t.i.d	Combination therapy for the treatment of adults and children with HIV
Ritonavir (norvir)	Adult: 600mg PO b.i.d Pediatric: 250mg/m2 PO b.i.d	Part of combination therapy for the treatment of adults and children with VIH
Saquinavir (Invirase	Adult: 1000mg PO b.i.d with ritonavir 100mg PO b.i.d	Treatment of adults with HIV as part of combination therapy
Tipranavir (aptivus)	Adult:500mg/d PO with 200mg ritonavir Pediatric: 14mg/kg PO b.i.d with ritonavir	Treatment of adults/ children with HIV in combination with ritonavir

INTEGRASE STRAND TRANSFER INHIBITORS

HIV integrase strand transfer inhibitors (INSTIs), or simply integrase inhibitors, target HIV by terminating the integration of HIV into DNA. Integrase is one of three viral enzymes needed for HIV replication. As its name implies, integrase inserts HIV genetic material into the DNA of CD4 cells. By inhibiting integrase, these drugs prevent insertion of HIV DNA and thereby stop HIV replication. They are effective against both HIV-1 and HIV-2.

We currently have three approved INSTIs: raltegravir, dolutegravir, and elvitegravir. All are indicated for combined use with other antiretroviral agents to treat adults infected with HIV-1.



Raltegravir

Actions and Use

Raltegravir [Isentress] was the first HIV integrase strand transfer inhibitor to be developed. Raltegravir stops HIV replication by preventing insertion of HIV DNA. Raltegravir is active against HIV strains resistant to some of the other drugs. Raltegravir was originally approved only for treatmentexperienced patients but is now approved for treatment-naïve patients as well. In current guidelines, raltegravir (in combination with tenofovir plus either emtricitabine or lamivudine) is considered a first-choice drug for HIV treatment. In clinical trials, raltegravir demonstrated increased viral suppression when compared to protease inhibitors and the NNRTI efavirenz. Unfortunately, HIV resistance was also more likely to develop.

Adverse Effects

Raltegravir is generally well tolerated by most. The most common adverse effect is an elevation in liver enzymes that occurs in about 10% of those taking the drug. Approximately 4% to 5% will have elevations in serum amylase and lipase. Symptomatic adverse effects occur infrequently. In fact, the most common adverse effects, insomnia and headache, occur in only 2% to 4% of those taking this drug. In clinical trials, a few patients experienced myopathy and rhabdomyolysis, but a causal relationship has not been established. Rarely, patients have developed severe hypersensitivity reactions. Skin reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis, which can be fatal. Organ dysfunction, including liver failure, may also develop.

Patients who develop signs of a hypersensitivity reaction (e.g., severe rash, or rash associated with blisters, fever, malaise, fatigue, oral lesions, facial edema, hepatitis, angioedema, muscle or joint aches) should discontinue raltegravir immediately.

Contraindications

There are no contraindications to taking raltegravir. Those with pre-existing hepatic impairment may be at risk for worsening of this condition. Caution should be maintained when taken by patients with a history of rhabdomyolysis or by those taking other drugs that have this adverse effect.

Drug Interactions

Because raltegravir is metabolized by glucuronidation, it does not have as many drug interactions as those with roles in P450 enzyme systems. Atazanavir and other inhibitors of UGT can increase levels of raltegravir. Conversely, inducers of UGT (e.g., efavirenz, fosamprenavir, rifabutin, tipranavir) can lower raltegravir levels.

HIV FUSION INHIBITORS

Unlike most other drugs for HIV, which inhibit essential viral enzymes (i.e., reverse transcriptase, integrase, protease), HIV fusion inhibitors block entry of HIV into CD4 T cells. Earlier in the chapter, we discussed the replication cycle of HIV. Recall that in step 2, the lipid bilayer envelope of HIV fuses with the lipid bilayer of the host cell membrane. HIV fusion inhibitors block this fusion process.

Enfuvirtide

Enfuvirtide [Fuzeon], widely known as T-20, is the first and only HIV fusion inhibitor currently approved by the FDA. Unfortunately, although enfuvirtide is effective, it is also inconvenient (treatment requires twice-daily subQ injections) and very expensive (treatment costs about $52,000 a year). Furthermore, injection-site reactions occur in nearly all patients.

Mechanism of Action

Enfuvirtide prevents the HIV envelope from fusing with the cell membrane of CD4 cells, and thereby blocks viral entry and replication. Fusion inhibition results from binding of enfuvirtide to gp41, a subunit of the glycoproteins embedded in the HIV envelope (see Fig. 94.1). As a result of enfuvirtide binding, the glycoprotein becomes rigid, and hence cannot undergo the configurational change needed to permit fusion of HIV with the cell membrane.

Resistance

Resistance to enfuvirtide has developed in cultured cells and in patients. The cause is a structural change in gp41. In clinical trials, reductions in drug susceptibility have ranged from 4- to 422-fold. Fortunately, the HIV mutations that confer resistance to enfuvirtide do not confer cross-resistance to NRTIs, NNRTIs, PIs, INSTIs, or CCR5 antagonists. Conversely, resistance to NRTIs, NNRTIs, PIs, INSTIs, or CCR5 antagonists does not confer cross-resistance to enfuvirtide. The rate at which resistance develops depends on the efficacy of the drugs used concurrently. When the patient's other antiretroviral drugs are still effective, resistance to enfuvirtide develops relatively slowly. However, when there is significant resistance to the other drugs, resistance to enfuvirtide develops rapidly.

Therapeutic use

Use Enfuvirtide is reserved for treating HIV-1 infection that has become resistant to other antiretroviral agents. Specifically, the drug is indicated for HIV-1 infection in patients who are treatment experienced and have evidence of HIV replication despite ongoing ART. To delay emergence of resistance, enfuvirtide should always be combined with other antiretroviral drugs.

Adverse Effects

They include injection-site reactions, pneumonia, and hypersensitivity reactions.

Drug Interactions

Enfuvirtide appears devoid of significant drug interactions. There are no interactions with other antiretroviral drugs that would require a dosage adjustment for either enfuvirtide or the other agent.

Table 5.1.4: INTEGRASE INHIBITORS

Drug name	Dosage/route	Usual indications
Fusion inhibitor		
Enfuvirtide (fuzeon)	Adult: 90mg b.i.d by subcutaneous injection Pediatric(6-12 years): 2mg/kg b.i.d by subcutaneous injection	Part of combination therapy for the treatment of HIV patients with evidence of VIH replication with ritonavir
Integrase inhibitor		
Dolutegravir (tivicay)	Adult and children weighing at least 40kg: 50mg/d PO in combination with other antiretrovirals	Part of combination therapy for the treatment of infections
Raltegravir (Isentress)	Adult, child 12 years and older: 400mg PO b.i.d Pediatric (6-12 years): 400mg PO b.i.d or 300mg b.i.d chewable tablet Other pediatric dosage based on weight	Part of combination therapy for the treatment of infections

CCR5 ANTAGONISTS

CCR5 antagonists, like the fusion inhibitors, block entry of HIV into CD4 T cells. However, the mechanism by which they accomplish this is different.

Maraviroc

Maraviroc [Selzentry, Celsentri] is the first, and currently only, representative of the CCR5 antagonists. Maraviroc isn't usually used for initial treatment of HIV. It appears most effective in treating patients with drug-resistant HIV.

Mechanism of Action

CCR5 is a co-receptor that some strains of HIV must bind with to enter CD4 cells. Maraviroc binds with CCR5 and thereby blocks viral entry. HIV strains that require CCR5 for entry are referred to as being CCR5 tropic. Between 50% and 60% of patients are infected with this type of HIV. Maraviroc and enfuvirtide (a fusion inhibitor) are the only antiretroviral drugs that block HIV entry.

Therapeutic Use

Maraviroc is indicated for combined use with other antiretroviral agents to treat patients age 16 years and older who are infected with CCR5-tropic HIV-1 strains. The drug was originally approved only for treatment-experienced patients but is now approved for treatment-naïve patients as well. Before maraviroc is used, a test must be performed to confirm that the infecting HIV strain is CCR5 tropic.

Adverse Effects

The most common side effects are cough, dizziness, pyrexia, rash, abdominal pain, musculoskeletal symptoms, and upper respiratory tract infections. Intensity is generally mild to moderate. Liver injury has been seen in some patients and may be preceded by signs of an allergic reaction (e.g., eosinophilia, pruritic rash, elevated immunoglobulin E).

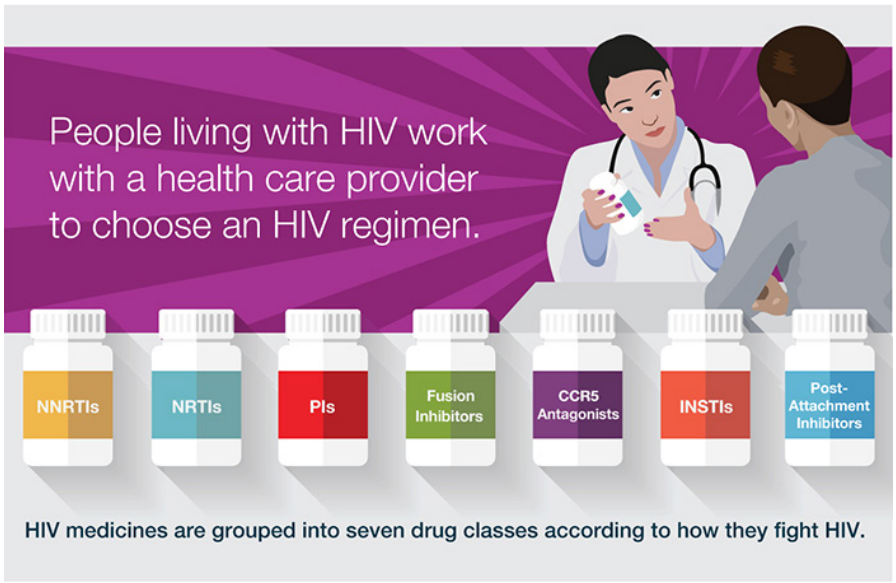
Patients should be informed about signs of an evolving reaction (itchy rash, jaundice, vomiting, and/or abdominal pain) and instructed to stop maraviroc and seek medical attention. During clinical trials, a few patients experienced cardiovascular events, including myocardial ischemia and MI. Maraviroc should be used with caution in patients with cardiovascular risk factors.

Drug Interactions

Because maraviroc is metabolized by CYP3A4, drugs that inhibit or induce this enzyme will affect maraviroc levels. Levels will be raised by strong CYP3A4 inhibitors, including protease inhibitors (except tipranavir/ritonavir) and delavirdine. Conversely, maraviroc levels will be lowered by strong CYP3A4 inducers, including etravirine and efavirenz. As always, it is important to check for interactions via a comprehensive database before administering drugs such as this one.

Table 5.1.5: FUSIOIN INHIBITORS

Drug name	Dosage/route	Usual indications
Fusion inhibitor		
Enfuvirtide (fuzeon)	Adult: 90mg b.i.d by subcutaneous injection Pediatric(6-12 years): 2mg/kg b.i.d by subcutaneous injection	Part of combination therapy for the treatment of HIV patients with evidence of VIH replication with ritonavir
CCR5 Coreceptor antagonist		
Maraviroc (selzentry)	Adult: 150mg PO b.i.d ; dosage may need to be adjusted based on other drugs in the regimen	Part of combination therapy for the treatment of infections
Integrase inhibitor		
Dolutegravir (tivicay)	Adult and children weighing at least 40kg: 50mg/d PO in combination with other antiretrovirals	Part of combination therapy for the treatment of infections
Raltegravir (Isentress)	Adult, child 12 years and older: 400mg PO b.i.d Pediatric (6-12 years): 400mg PO b.i.d or 300mg b.i.d chewable tablet Other pediatric dosage based on weight	Part of combination therapy for the treatment of infections



Self-assessment 5.2

1) Why is combination therapy necessary in HIV treatment?
2) Which of the following antiretroviral drugs is classified in the protease inhibitors?
   a) Enfuvirtide
   b) Raltegravir
   c) Atazanavir
   d) Nevirapine
3) What is the mechanism of action of enfuvirtide?

5.3. Antiretroviral treatment in adolescents and adults

Learning Activity 5.3

A 33-year-old newly diagnosed HIV patient was advised to start antiretroviral treatment at ART sevice where you are appointed as an associate nurse. During pre-treatment counselling, you focus on the number of combined medications to use.

1) What is the number of medications combinations is required to use in HIV/AIDS management?
2) What should the nurse include in the teaching as the ideal time to initiate ARVs after HIV diagnosis?

CONTENT SUMMARY

People with HIV should take medicine to treat HIV as soon as possible. HIV medicine reduces the amount of HIV in the body (**viral load**) to a very low level, which keeps the immune system working and prevents illness. It can even make the viral load so low that a test can't detect it. This is called an **undetectable viral load**. Getting and keeping an undetectable viral load* is the best thing people with HIV can do to stay healthy.

Initiating Antiretroviral Therapy: ART regimens typically contain at least three drugs. Regimens that contain only two drugs are not generally recommended, and monotherapy should always be avoided, except possibly during pregnancy. Additionally, all ART regimens contain drugs from at least two different classes. By using drugs from different classes, we can attack HIV in two different ways (e.g., inhibition of reverse transcriptase and inhibition of protease) and can thereby enhance antiviral effects.

Criteria for Eligibility to ART in Adults and adolescent: Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality and to prevent the transmission of HIV to others. The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV.

In addition to enhancing antiviral effects, the use of multiple drugs reduces the risk for resistance. Resistance reduction occurs because the probability that HIV will undergo a mutation that confers simultaneous resistance to three or four drugs is much smaller than the probability of undergoing a mutation that confers resistance to just one drug.

Below are key considerations in clinical management of adolescents and adults living with HIV:

- Clinical and laboratory evaluations are the cornerstones of care and treatment of HIV positive adolescents and adults.
- Renal creatinine clearance is mandatory for adolescents and adults since they initiate with TDF based regimen.
- Viral load monitoring should be conducted at 6 months and at 12 months after ART initiation, and annually thereafter. DTG-based regimen remains the preferred first-line option.
- TDF/3TC/EFV600mg is the alternative first-line regimen for adults and adolescents who cannot take TLD

- DTG-based regimen is the preferred 2nd line option for patients failing a non-DTG 1st line regimen.
- For patients failing DTG-based regimen, specialist consultation and genotyping should be considered.
- PLHIV with advanced HIV disease should be offered a package of interventions including screening, treatment and/or prophylaxis for major OIs, rapid ART initiation and intensified adherence support.
- TB screening should be done at enrolment and at each clinical visit
- Cotrimoxazole should be given to patients with advanced diseases.

Clinical evaluation

- Present and past medical history
- Comprehensive physical examination
- WHO staging
- Drug history
- Sexual history
- Nutrition status assessment
- OI screening (e.g. TB)
- NCDs screening mainly (Refer annex V).
- Cardiovascular disease: blood pressure, cardiomyopathies
- Malignancies: cervical cancer, breast cancer
- Metabolic diseases: diabetes, hyperlipidemia, hypocholesteremia
- Mental health illness

Laboratory evaluation Baseline:

- CD4 cell count,
- Cryptococcus antigen (if CD4 count < 200 cells/mm3)
- Renal function (creatinine and calculation of creatinine clearance)
- Hepatitis B surface antigen (Ag HBs)
- Hepatitis C antibody (HCV Ab)
- LFTs
- GeneXpert if TB screening is positive
- Additional investigations as clinically indicate

ART Regimen in adolescents and Adult

Treatment line	Preferred regimen	Alternative regimen
1st Line	2NRTI+Integrase Inhibitor	2NRTI+1NNRTI
2nd Line	2NRTI +1PI	2NRTI+Integrase Inhibitor
3rd Line	Optimized NRTI or ETV+1PI+1Integrase inhibitor based on genotyping results	

First line ART regimen options

There are two options recommended in first line regimen

DTG-based

NNRTI-based

Preferred 1st line regimen	Alternative 1st line regimen
*TDF/3TC/DTG	*TDF/3TC/EFV600
Note: *If TDF is contraindicated, replace with ABC	

Dosage and administration of first-line regimen

Dosage and administration of first-line regimen

Molecule	Dosage
Tenofovir (TDF)	300 mg once a day
Abacavir (ABC 300 mg twice a day or 600 mg once a day	
Lamivudine (3TC)	300 mg once a day
Dolutegravir (DTG)	50 mg once a day
Efavirenz (EFV)	600mg once evening

Prescription of ART first line regimen

1) TDF/3TC/DTG (300/300/50 mg) (OD)
2) ABC/3TC (600/300 mg) + DTG (50 mg) (OD)
3) TDF/3TC/EFV (300/300/400mg)
4) ABC/3TC (600/300mg) + EFV 600mg

Notes:

- Encourage taking EFV based regimens in the evening before 8:00 pm to minimize dizziness
- Patients with EFV associated side effects should be advised to take it either 1-2 hours before or after meals to minimize side effects

Management of treatment failure among adolescents and adults

The monitoring of ART response and identification of treatment failure are the same as for children

- For early management of treatment failure as well as second line treatment failure refer to the treatment failure algorithm in children section.

Recommended regimens for second-line ART

Recommended regimens for 2nd line ART in adults after failure of specific first line regimens

Failing first line	Preferred 2nd line	Alternative 2nd line
TDF/ABC+3TC+DTG	AZT+3TC+ATV/r (LPV/r)	Consider specialist consultation and/or genotyping
TDF/ABC+3TC+EFV	AZT+3TC+DTG	AZT+3TC+ATV/r(LPV/r)
TDF/ABC+3TC+ PIs	AZT+3TC+DTG	

If TDF is contraindicated, replace with ABC

In case of hepatitis B co-infection, maintain TDF: TDF+AZT/3TC+ATC/r or LPV/r

Recommended regimens for third-line

- DTG 50mg BID + Darunavir/ritonavir + Optimized NRTI or Etravirine can be used based on genotyping results
- The 3rd line regimen must only be given upon expert consultation and usually with the assistance of genotyping results.
- Before prescribing third-line therapy, the patient must undergo extensive

additional adherence counselling and should have a treatment partner involved in adherence assistance. Adherence counselling is critical to the success of this regimen.

- NRTI backbone may be necessary based on genotyping test or in case of Hepatitis B co-infection

Monitoring of adolescents and adults on ART

Clinical evaluation and laboratory tests play a key role in assessing adolescents and adults before ART initiation, and then monitoring their treatment response as well as possible toxicity of antiretrovirals. Note that once started, ART is a treatment for life but should be changed in the following cases:

- Drug toxicity
- Drug-drug interactions
- Co-infection
- Treatment failure confirmed by viral load

Notes:

- The follow up of CD4 count should be done whenever clinically indicated.
- For STIs management, refer to national guidelines for STIs and hepatitis.

1) TREATMENT FAILURE

Treatment failure is arguably the most compelling reason for changing the regimen. Failure is indicated if:

- Plasma HIV RNA remains above 200 copies/mL after 24 weeks
- Plasma HIV RNA remains above 50 copies/mL after 48 weeks
- Plasma HIV RNA rebounds after falling to an undetectable level
- CD4 T-cell counts continue to drop despite antiretroviral treatment
- Clinical disease progresses despite antiretroviral treatment

2) DRUG TOXICITY

If a patient experiences toxicity typical of a particular drug in the regimen, that drug should be withdrawn and replaced with a drug that is (1) from the same class and (2) of equal efficacy. For example, if a patient taking zidovudine were to develop anemia and neutropenia, zidovudine should be discontinued and replaced with another NRTI (e.g., stavudine). Note that when toxicity is the reason for altering the regimen, changing just one drug is proper, whereas when resistance or suboptimal treatment is the reason, at least two of the drugs should be changed.

3) Promoting Patient Adherence

To achieve treatment goals and delay emergence of resistance, strict adherence to the prescribed regimen is critical. Unfortunately, several factors: duration of

treatment, complex medication regimens, multiple adverse drug effects, drug-drug interactions, and drug-food interactions make adherence to ART challenging for patients.

The factors that predict poor adherence (e.g., poor clinician-patient relationship, active use of alcohol or street drugs, depression and other mental illnesses), as well as factors that predict good adherence (e.g., availability of emotional and practical support, ability to fit dosing into the daily routine, appreciation that poor adherence will cause treatment failure).

Self-assessment 5.3

1) What is the preferred 1st line regimen for adolescents and adults?
2) What is the alternative first-line regimen for adults and adolescents who cannot take TLD?
3) What can be done if a patient experiences toxicity typical of a particular drug in the regimen?

5.4. Antiretroviral treatment in Children

Learning Activity 5.4

You are an associate nurse and you receive a mother bringing her 2-year-old baby who was born with HIV. She wants the baby to be started on antiretroviral drugs, and there is a student in the clinical placement who doubts on the antiretroviral drugs to administer to the baby.

1) Which regimen should the baby start with?
2) The symptoms of HIV infection generally start later compared to the time it takes for adults to develop symptoms. TRUE or FALSE
3) The preferred 1st line ART option for children of 30kgs and above is ABC/3TC+LPV/r. TRUE or FALSE

CONTENT SUMMARY

In young children, the course of HIV infection is accelerated. Whereas adults generally remain symptom free for a decade or more, many children develop symptoms by their first birthday. Death often ensues by age 5 even with ART. Why do young children succumb so quickly?

Primarily because their immune systems are immature, and hence less able to fend off the virus. Because immune function is limited, levels of HIV RNA climb higher in toddlers than in adults, and then decline at a much slower rate.

In very young patients, diagnosis and monitoring of HIV infection employs different

methods than those used in adolescents and adults. In particular, for infants under 18 months of age, diagnosis should be based on viral load assays, not on antibody tests. For children under 5 years of age, monitoring of immune status should be based on the percentage of CD4 cells, not on absolute CD4 counts.

Like older patients, young patients should be treated with a combination of antiretroviral drugs, with the goals of (1) reducing plasma viral HIV to an undetectable level and (2) stabilizing or improving immune status.

Clinical and laboratory evaluations are the cornerstones of care and treatment of HIV positive children of ≤10 years old. DTG is used for children with weight ≥ 20kgs. The preferred 1st line option for children less than 20kg is ABC/3TC+LPV/r. The preferred 1st line option for children of ≥ 20kg ABC/3TC+DTG. The preferred 1st line option for children of 30kgs and above without renal failure is TDF/3TC/DTG. For children on LPV/r, the preferred formulation is pellet (40mg/10mg, oral pellet) due to its storage and palatability reasons.

For children with more than 15kg, ATV/r can be used to replace LPV/r. For children on ABC/3TC, 120/60mg is the preferred strength. ABC is contra-indicated for children less than 3 months. If HIV is confirmed before 3 months, the recommended 1st line ART regimen is AZT+3TC+LPV/r. Switch to AZT-based regimen in case of intolerance to ABC. LPV/r is contra-indicated for new-born less than 15 days. If switching from AZT-based regimen, consider VL (viral load) suppression. If treatment failure, consider second line regimen.

TB screening is mandatory for all children at enrolment and at each clinical visit. TPT (Tuberculosis preventive therapy) should be integrated in HIV management. IPT (Isoniazid preventive therapy: Isoniazid 10mg/Kg) is used for 6 Months to all HIV children of ≤5 years old without active TB but with a history of TB contact. Anti-TB should be initiated immediately and ART within 2 to 8 weeks. The treatment failure (TF) is defined by the virological failure (plasma viral load >1000 copies/ml) based on two consecutive viral load measurements after 3 months with intensive adherence support. The management of 1st line TF is done after identifying its probable cause and then act as shown by figure 7. The recognition of 2nd line TF is similar to the 1st line TF and the shift to 3rd line is guided by genotyping and expert consultation. The monitoring of children on ART encompasses clinical and laboratory monitoring in order to assess treatment response and potential drug toxicity.

ART Regimen for children younger than 10 years of age

Table 5.4.1 First line options for ART regimen in children:

Treatment weight range	Preferred regimen		Alternative Regimen	Comments
CHILDREN LIVING WITH HIV INITIATING ART				
<20 kg	ABC sp+3TC sp+LPV/r (40mg/10mg)pt Or ABC+3TC+LPV/r (Syrups)		ABC+3TC+NVPsp/ EFV	If less than 20kg, a child should stay on LPV/r until he reaches 20kg and shift to DTG. EFV is for children of ≥ 3 years
≥ 20 kg	20-30 kg	ABC+3TC+DTG	ABC+3TC+EFV	When reaching 30 kg, a child should be transitioned to TDF+3TC+DTG
	>30 kg	TDF+3TC+DTG	TDF+3TC+EFV	If renal impairment, consider ABC.

Table 5.1.2: Initiation of ART in children

Current regimen	Weight band	Optimal regimen for transition	Comments
CHILDREN LIVING WITH HIV ALREADY ON ART			
ABC +3TC +EFV	<20kg	No change ABC +3TC +EFV	If a child reaches 20kg shift to ABC +3TC +DTG
	20-30kg	ABC +3TC +DTG	If a child reaches 30kg shift to TDF +3TC +DTG
	>30kg	TDF +3TC =DTG	
ABC +3TC +LPV/r	<20kg	No change ABC +3TC +LPV/r	If a child raches 20kg shift to ABC + 3TC +DTG
	20-30kg	ABC +3TC +DTG	If a child reaches 30kg shift to TDF +3TC +DTG
	>30kg	TDF+3TC +DTG	

Table 5.1.3:Children who are already on ART

Second-line ART in Children

Falling first -line regimen	Preferred second-line regimen	Alternative second-line regimen	Comments
ABC or TDF +3TC +DTG	AZT + 3TC +LPV/r	HIV Expert opinion	ATV/r can be used as alternative to LPV/r for children ≥ 15kg
ABC or TDF + 3TC +LPV/r	HIV Expert opinion	AZT +3TC + DTG (in children≥ 20kg)	
ABC + 3TC + EFV	AZT + 3TC + DTG (in children ≥ 20kg)	AZT +3TC +LPV/r	ATV/r can be used as an alternative to to LPV/r for children ≥ 15kg

Self-assessment 5.4

1) When the HIV positive children should be screened for TB infection?
2) Which ART regimen should a 9-year-old child be started with?
3) Which of the following options is true with regard to treatment of patients with HIV and TB coinfection?

a) ART should be initiated immediately and anti-TB within 2 to 8 weeks
b) Anti-TB should be initiated immediately and ART within 2 to 8 weeks
c) ART should be initiated immediately and anti-TB within 6 weeks
d) Anti-TB should be initiated immediately and ART within 12 weeks

5.5. ARV Treatment in Pregnant Women

Learning Activity 5.5

A woman of 25 years of age was diagnosed for HIV positive during antenatal care at the health center. According to WHO/CDC, it is recommended that all HIV positive women should take ARTs.

Read the pharmacology book and respond the following questions

1) When a pregnant woman newly diagnosed HIV positive should start the treatment?
2) What is the ART regimen for an HIV positive pregnant woman?

CONTENT SUMMARY

In general, the management of HIV infection in pregnant women should follow the same guidelines for managing HIV infection in nonpregnant adults. Accordingly, current guidelines recommend ART for all pregnant HIV-infected women. ART is needed not only for maternal health, but also to reduce the risk for perinatal HIV transmission.

Drug selection is challenging in that information on pharmacokinetics and safety during pregnancy is limited.

When treating HIV infection in pregnant women, the goal is to balance the benefits of treatment, reducing viral load, thereby promoting the health of the mother and decreasing the risk for vertical HIV transmission (i.e., transmission to the foetus) against the risks of drug-induced fetal harm (e.g., teratogenesis, lactic acidosis, death). As a rule, the benefits of treatment outweigh the risks.

The primary determinants of therapy are the clinical, virologic, and immunologic status of the mother; pregnancy is a secondary consideration. Nonetheless, pregnancy should not be ignored.

Routine HIV testing for all pregnant women attending ANC for first time during current pregnancy together with their male partners (unless already known HIV positive status). It is preferable that these services are offered during the first trimester of pregnancy but they should be ongoing until delivery.

Every HIV-positive woman will be provided with specific counselling on family planning and getan access to a family planning method of her choice.

HIV positive pregnant and breastfeeding women should be offered index testing, partner notification and family testing services.

Every pregnant woman whose HIV status is unknown during ANC should be tested for HIV at the time of delivery.

Every pregnant woman who tested HIV negative during ANC should be retested at the time of delivery. Thereafter, retesting during postnatal period will be based on HIV risk assessment outcomes.

Women tested HIV positive during ANC or at the time of labor, should start anti-retroviral therapy immediately. In case of delay, ART initiation should not go beyond 7days.

Every pregnant or breastfeeding woman newly tested positive for HIV should start with ART regimen Tenofovir + Lamivudine + Dolutegravir.

Every pregnant or breastfeeding woman newly tested HIV-positive and on ART, should receive the first viral load test three months after ART initiation and then after every six months until the end of PMTCT follow up.

All infants born to a known HIV positive mother should receive ART prophylaxis with zidovudine and Nevirapine immediately. If not done immediately, it should be in first 72 hours post-partum or as soon as possible during the first six weeks of life.

All HIV exposed or infected children should have regular growth monitoring to enable early detection of growth retardation and undertake appropriate management.

Pre exposure prophylaxis is offered in the context of PMTCT to HIV negative pregnant and/or breastfeeding women in the following circumstances:

- Women in discordant relationship whose partners are either not on ART or are on ART but not virally suppressed
- Women practicing sex work

The regimen recommended for PrEP is a once daily TRUVADA or Tenofovir and Lamivudine for the entire pregnancy and breastfeeding period.

The use of ART for HIV positive pregnant women will depend on whether she was already on ART or not. The following situations are possible during pregnancy:

c) If the HIV-Positive pregnant woman is already initiated on ART, consider the following aspects:

- Adherence to the current ART regimen
- Viral load suppression as per the most recent viral load test results
- Consider viral load result as ‘recent’ if it was performed less than six months prior to the firstANC visit.
- It is mandatory to repeat the viral load test for all pregnant women not tested at the firstANC, before the third term of pregnancy (preferably at 6 months of pregnancy)
- If the woman is virally suppressed, she will be kept on her current ART regimen.

- If the woman is not virally suppressed (>200 copies/ml), she will be switched to a Dolutegravir based regimen plus two NRTIs.
- The switch to Dolutegravir- based regimen will be conducted concurrently with the adherence counselling for patients with documented poor adherence.

d) If a woman is newly diagnosed HIV positive during pregnancy:

- The woman is immediately enrolled in care and initiated on ART
- The preferred ART regimen is Tenofovir + Lamivudine + Dolutegravir (TDF+3TC+DTG)
- Any woman with impaired renal function or any contraindication to TDF will receive ABC + 3TC+DTG

NOTE: Doses are the same as in non-pregnant adults' HIV treatment. Monitoring of renal function is important.

Self-assessment 5.5

1) Any pregnant woman whose HIV status is unknown during ANC doesn't need to be tested for HIV at the time of delivery. TRUE or FALSE
2) Given their fragile status, the pregnant women with HIV positive status should benefit from lower doses of ARTs compared to the non-pregnant adults. TRUE or FALSE
3) Which of the following treatment regimens is used as ART initiation among pregnant women in Rwanda?

   a) Abacavir + Lamivudine + Dolutegravir.

   b) Tenofovir + Lamivudine + Dolutegravir.

   c) Efavirenz + Lamivudine + Dolutegravir.

   d) Nevirapine + Lamivudine + Dolutegravir.

5.6. Prophylaxis in new-borns with Perinatal HIV Exposure or HIV Infection

Learning Activity 5.6

Visit library and read pharmacology books /use internet and respond to following question:

When should the newborn exposed perinatally to HIV start taking newborn ARV regimens?

CONTENT SUMMARY

A child is considered as 'exposed to HIV', if he/she is born to an HIV positive mother. The initiation of infant prophylaxis depends on the time the mother was diagnosed HIV positive. Children born to HIV negative mothers in discordant couple will not receive any prophylaxis as long as their mothers remain HIV negative.

Infant born to a known HIV-positive mother:

All children born to a known HIV positive mother (before or during labour) will receive zidovudine and Nevirapine (AZT+ NVP) as soon as possible within 72 hours after birth up to six weeks of life. The baby will also start cotrimoxazole prophylaxis at the age of 6 weeks until the final confirmation of HIV negative status at the age of 24 months.

Infant born to a mother diagnosed for HIV after delivery

If the mother is identified to be HIV-positive at the time of breastfeeding, she should be put on ART. The child will start a combined AZT and NVP as soon as possible for six weeks. At the end of 6 weeks ART prophylaxis; the child will also start cotrimoxazole prophylaxis until the final confirmation of HIV negative status at 24 months of life.

All Breastfed infants who are at high risk of acquiring HIV, including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using NVP and AZT.

High-risk infants are defined as:

Infant born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; or born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load measurement available; OR identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

Self-assessment 5.6

1) During clinical practice in maternity ward, you receive a woman with baby at the second day of home delivery. You take blood sample for HIV testing. After 3 hours you receive a laboratory technician' s call informing you that the mother is HIV positive. Explain the management of mother and her baby to prevent mother to child transmission.

5.7. HIV Prevention among Discordant Couples

Learning Activity 5.7

1) A couple consults the healthcare facility where you are carrying out the clinical placement, and they report they are discordant. The senior nurse tasks you to explain to the couple the overall interventions package for that discordant couple. What is that package?
2) What are the objectives of these interventions?

CONTENT SUMMARY

Evidence-based interventions package for HIV sero-discordant couples can be provided through facility based and/or community interventions. Although these interventions are delivered in a package, providers must ensure that they contextualize the specific, particular needs of the couple since different couples may have different needs.

The objectives of these interventions are:

- To protect the negative partners from acquiring HIV infection
- To provide care and treatment to HIV positive partners, allowing them access to early treatment that improves clinical outcomes
- To protect future children from HIV infections
- To offer the appropriate HIV prevention package for children and other family members of the HIV positive individuals
- To support the prevention of unwanted pregnancies in discordant couples

The overall intervention package for discordant couples consists of the following:

- Risk reduction counselling and condom provision
- Initiation of pre-exposure prophylaxis for those whose HIV positive partner is not yet on ARV or are not virally suppressed
- Family planning counselling and service provision
- Repeat HIV testing for the uninfected partner every 12 months
- Care and treatment for the HIV-positive partner
- STI screening and treatment

In case of a pregnant HIV-negative partner:

- The HIV testing shall be done every three months
- A pre-exposure prophylaxis should be offered in case of non-viral suppression for the positive partner.
- At labor a single dose of TDF+3TC+DTG will be offered for all women who are not taking the pre-exposure prophylaxis.

The health care provider should encourage the discordant couple to follow up in the same health facility and synchronize with pharmacy refills and appointment schedule. Ongoing psychosocial support and counselling shall be offered to the discordant couple.

Self-assessment 5.7

1) The health care provider should encourage the discordant couple to follow up in the same health facility and synchronize with pharmacy refills and appointment schedule. TRUE or FALSE
2) Pregnant HIV-negative partner in discordant couples should receive a single dose of TDF+3TC+DTG at labor if they are not taking the pre-exposure prophylaxis. TRUE or FALSE

5.8. ART for Post-Exposure Prophylaxis (PEP)

Learning Activity 5.8

3) While he was giving IM injection to a known HIV positive patient, an associate nurse injured himself with a needle after injecting the drug. The senior nurse sends him to the ART service for post exposure prophylaxis. Which drugs may preferably be administered to this patient?
4) An HIV serology test should be performed for the exposed caregiver as soon as possible (ideally within 72 hours). TRUE or FALSE

CONTENT SUMMARY

Every person who has experienced exposure to blood/body fluids, victim of sexual assault, or accidental sexual exposure (i.e., condomless, sex with a known HIV-positive person; condom breakage) must have access to an early evaluation of the risk of HIV infection and antiretroviral prophylaxis if indicated. It is therefore necessary to have PEP services. Evidence shows that initiating ART prophylaxis soon after exposure to HIV reduces the risk of HIV infection by about 80%. Postexposure prophylaxis (PEP) is short-term ART to reduce the likelihood of acquiring HIV infection after potential exposure.

Post-exposure prophylaxis should be provided immediately or preferably within 72 hours of exposure. An HIV serology test should be performed on the exposed individual as soon as possible (ideally within 48 hours).

Case of Accidental Exposure to Blood (AEB) or Other Biological Fluids

In case of accidental exposure to blood, always clean the exposed area immediately. In case of exposure through needle stick or skin injury, clean the wound immediately

with clean water and soap. In case of splash on the mucous membranes (particularly the conjunctiva), rinse at least for 5 minutes with copious amounts of water or preferably physiological saline or any available saline and do not apply disinfectant on the mucous membranes. One of the health care providers from the health facility must evaluate the actual risk for a given patient. This evaluation includes:

- The severity of the exposure, which is directly linked to the depth of the wound and the type of needle that was responsible for the injury (venipuncture needle, needle for injection, non sharp instrument).
- For external contact of secretions with the skin or mucosa (splash), the risk is higher with blood than with any other body secretions (amniotic fluid, serous fluid). The person assumed to be the source should be assessed on his or her HIV status, clinical and immunological status and history of ART. If the HIV status is not known, it is important to establish it with his/her free consent. If the HIV status of the source person cannot be obtained within 4 hours, prophylaxis for the exposed person should be started immediately after a negative HIV test. If eventually the person assumed to be the source is proven to be HIV-negative, then ARV prophylactic treatment may be stopped

Case of Sexual Assault or Rape

In case of rape, the provider must first follow the HIV counselling and testing.PEP should be offered to the sexual assault victim once the clinician has assessed all the factors involved in the likelihood of HIV transmission (suspicion of HIV positivity in the assailant, probability of HIV transmission). PEP might help the victim gain a sense of control and decrease their anxiety about acquiring HIV. Consider HIV post-exposure prophylaxis for survivors of sexual assault presenting within 72 hours of the assault. In addition to HIV post-exposure prophylaxis, women should be offered emergency contraception to prevent unintended pregnancy immediately or preferably within 72 hours after sexual exposure.

ART Prophylaxis in PEP

The current recommended duration of post-exposure prophylaxis for HIV infection is 28 days. Treatment should start as early as possible, within the first 4 hours following the exposure, without waiting for results of HIV serology of the source person. A limit of 72 hours is reasonable in seeking maximum efficacy, however the sooner the better.

The recommended post-exposure prophylaxis drugs are based on the current second and first line regimen:

1.TDF+ 3TC / FTC +ATV/r

2. AZT + 3TC/ FTC + ATV/r(If noTDFor a contraindication)

NB: The recommended ART Prophylaxis is the same in rape/sexual assault and exposure to biological fluids

Self-assessment 5.8

1) When HIV post-exposure prophylaxis for survivors of sexual assault is taken into consideration?
2) What are the actual risks the health care providers from the health facility must evaluate in case of exposure through needle stick or skin injury?

5.9. End unit assessment

End of unit assessment

I. Complete the empty spaces with the appropriate terms.

a) Antiretroviral drugs

b) Antiviral

c) Retrovirus

1) ……An agent that kills a virus or that suppresses its ability to replicate and, hence, inhibits its capability to multiply and reproduce.
2) ……is a group of viruses that belong to the family Retroviridae and that characteristically carry their genetic blueprint in the form of ribonucleic acid (RNA).
3) …….. are the drugs that are used to fight retrovirus infections which mainly include HIV. Different classes of antiretroviral drugs act on different stages of the HIV life cycle.

II. Respond by true or false

1) Abacavir (Ziagen), lamivudine (Epivir) and stavudine (Zerit XR), tenofovir (Viread).
2) Efavirenz (Sustiva), nevirapine (Viramune) are drugs in the class of protease inhibitors
3) Abacavir (Ziagen) lamivudine (Epivir), stavudine (Zerit XR), tenofovir (Viread), and zidovudine (Retrovir) drugs in the class of Nonnucleoside reverse transcriptase inhibitors .
4) Atazanavir, indinavir and lopinavirare drugs in protease inhibitors.
5) Like older patients, HIV positive young patients should be treated with a combination of antiretroviral drugs.
6) Antiretroviral therapy (ART) is recommended for all persons with HIV to cure the patient by killing the virus.

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