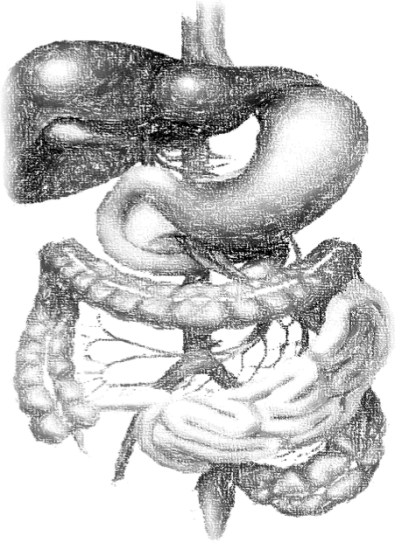
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



3: Treatment of dysentery and amebiasis

objectives

- To understand different causes of dysentery.
- To describe different classes of drugs used in treatment of both bacillary dysentery and amebic dysentery.
- To be able to describe actions, side effects of drugs for treating bacillary dysentery.
- To understand the pharmacokinetics, actions, clinical applications and side effects of antiamebic drugs.
- To be able to differentiate between types of antiamebic drugs; luminal amebicides, and tissue amebicide.

Color index

- extra information and further explanation
- important
- doctors notes
- Drug names
- Mnemonics

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري

Kindly check the editing file before studying this document

Dysentery

Definition

It is an inflammatory disorder of the intestine, especially of the colon, that results in severe diarrhea containing **mucus** and/or **blood in the feces** with **fever** and **abdominal pain** caused by any kind of infection.

Causes of Dysentery

Dysentery results from **viral** infections, **bacterial** infections, or **parasitic** infestations.

Bacillary dysentery **(bacterial infection mainly by shigella).**

The two most common causes

Amebic dysentery **(protozoal infection mainly by Entameba Histolytica).**

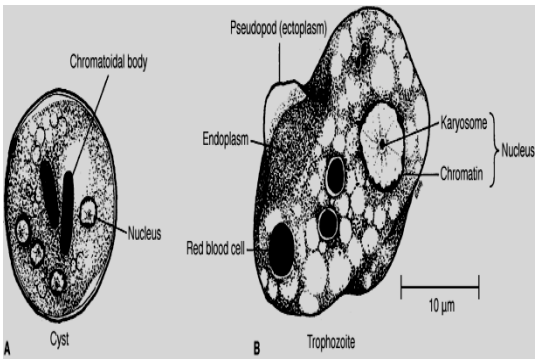
Treatment

- Maintain **fluid intake** (Rehydration) by using oral rehydration therapy or intravenous fluid therapy to avoid electrolytes imbalance.
- **Antimicrobial agents** should not be given until stool analysis is done to specify the etiological agent.
- **Anti diarrheal drugs** are contraindicated because they delay fecal excretion that can prolong fever (diphenoxylate or loperamide). if the diarrhea is inflammatory diarrhea we should not give ani-diarrheal drugs Why? Because When you decreasing GI motility → retaining the organism (not excreted from the body by feces)

Amebiasis

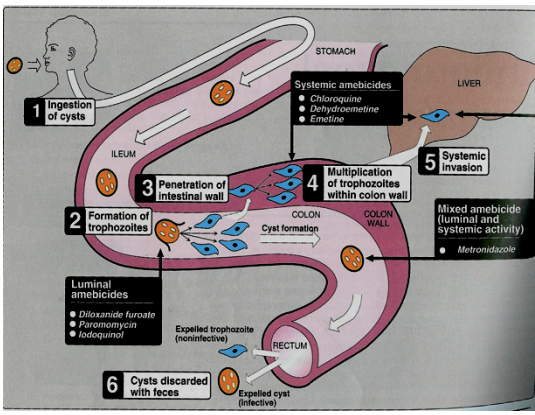
Definition

- Amebiasis is a **protozoal infection** of the intestinal tract that occurs due to ingestion of foods or water contaminated with **cysts** of **Entameba Histolytica**.
- The patients show varying degrees of illness from no symptoms to mild diarrhea to severe dysentery.



Life Cycle

1. Cysts ingestion in contaminated food or water.
2. Liberation of trophozoites in the colon.
3. Invasion of intestinal wall.
4. Multiplication of trophozoites within colon wall.
5. Systemic invasion to other organs (liver, lungs, brain).
6. Cyst formation in rectum and excretion in feces which Could be a source of infection to other



Entamoeba histolytica exists in two forms

1.Cysts (infective stage):

- can survive outside the human body.
- When ingested, liberate trophozoites in the lumen of the intestine.

2.Trophozoites (non-infective; invasive stage):

- Multiply and feed on intestinal bacterial flora.
- They may invade and ulcerate wall of large intestine or may migrate to liver or other tissues.
- In **rectum**, trophozoites transform to cysts and are excreted in feces.

Clinical presentations

- The patients show varying degree of illness from no symptoms to mild diarrhea to severe dysentery.
- Asymptomatic intestinal infection (**Carriers**, **passing cysts in stool**)
- Mild to moderate intestinal disease (**colitis**)
- Severe intestinal infection (**amoebic dysentery**)
- Ameboma **(localized granulomatous lesion of colon).**
- Hepatic abscess, and other extra-intestinal diseases.

ANTIAMEBIC DRUGS

Divided into two types:

Luminal amebicides

Not treated systematically

- Acts on the parasites in the lumen of the bowel. the drugs should not be absorbed (go out the GIT) to give its action at the site of infection (lumen)

- used for treatment of **asymptomatic** amebiasis (carriers). didn't invade the wall → the organism in the **cyst** form.
- used to eradicate cysts of E.histolytica after treatment of invasive disease

Incluede :

- Diloxanide furoate
- Iodoquinol

)parmo(برموا
)dil= اتفاقية (
)iodo(يا وأيدتها
)cysts(سيتي

Antibiotics

- Paromomycin can't be given orally because it is polar (aminoglycoside), so they are poorly absorbed
- Tetracycline

Tissue or systemic amebicides

- Act on ameba in tissues (trophozoites form) e.g. the intestinal wall and/or other extra-intestinal tissues as liver, brain and lung.

Used for treatment of systemic form of the disease (invasive amebiasis) e.g. intestinal wall infection or liver abscesses. After we finish treating the patient with these drugs we must give another course of luminal amebicides to eradicate the **cysts** in the lumen, so the cysts will not invade again and cause another infection

Include:

- **Metronidazole/ tinidazole**
- **Emetine** its name comes from its emetic effect which means vomiting, so if we give it to the patient it will induce vomiting **(dehydroemetine**
- **Chloroquine (liver only)**

)metro(ويسأل "المترو)travel = trophoztie(شخص مسافر
التاني)tini(حيجي امتى)emeti(كلو ينتظر الملكة
")chloroquine(

Tissue or systemic Amebicides

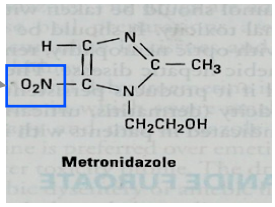
Drug

Metronidazole First choice

Action/Mech. of action

- Tissue amoebicide.
- Acts on trophozoites.
- Metronidazole inhibits DNA replication Of trophozoites –like **Ciprofloxacin-**
- Does not eradicate cysts from intestine because cysts are in the lumen, that's why after tissue amebicides course we must use luminal course to eradicate the cysts
- Drug of choice for treating invasive amebic infections (intestinal & extra-intestinal amebiasis).

The NO_2 will react with the DNA of the microbes and destroy it



Pharmacokinetics

- Given orally or IV we use it as IV with patients who have vomiting
- Absorption is rapid and complete (it is high lipid soluble).
- Wide distribution to all tissues and body fluids (CSF, saliva, milk) because of the pervious point
- Plasma half life is **(8 h)** so we have to repeat the dose
- Metabolized in liver (by CYP-450) by mixed function oxidase -first phase- followed by glucuronidation –second phase- (consider drug interactions).
- Excreted in urine. (should be used with precaution with kidney & liver diseases.)
- Clearance is decreased in liver impairment

Clinical Uses

- Extra-luminal amoebiasis: is the drug of choice in all tissue amebiasis N.B. should be followed by luminal amebicides.
- Giardiasis
- Trichomoniasis
- Broad spectrum of anaerobic bacterial infections used in dentil practice
- Peptic ulcer (Helicobacter pylori)
- Pseudo-membranous colitis (Clostridium difficile).

ADRs

GIT:

- Dry mouth (infection may result from the dryness of mouth)

Metro trains are made of metal (metal =metallic)

- Metallic taste (bad taste) which will lead to Nausea, vomiting, diarrhea (NVD)
- Oral Thrush (Moniliasis, yeast infection –one of the complication is fungal infection-)

CNS: Neurotoxicological effect (C.I. with epileptic patients)

- Insomnia, dizziness
- Peripheral neuropathy, paresthesia
- Encephalopathy, convulsion (IV infusion because there will be high conc. In the blood and may cross BBB, rare)

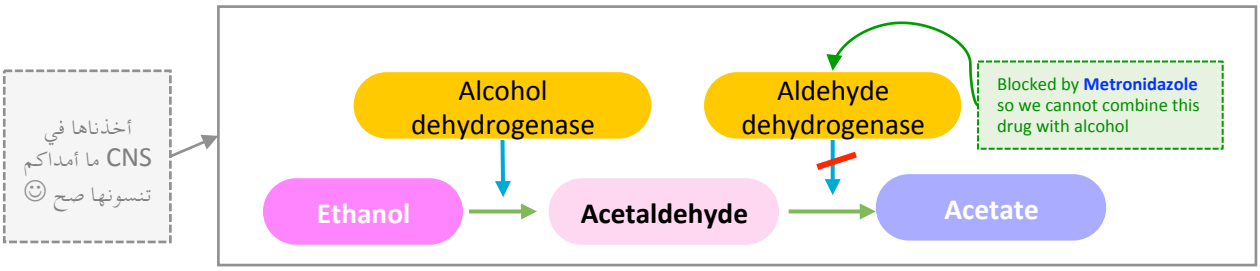
- **Dysuria, dark urine.**
- **Disulfiram-like effect** if taken with alcohol. more explanation in the next slide
- Neutropenia (low neutrophils), Reversible

Tissue or systemic Amebicides

Drug: Metronidazole

Drug – Alcohol Interaction

Combining metronidazole and alcohol causes nausea, vomiting, abdominal distress, flushing, headache, tachycardia, hyperventilation



Drug interactions

- CYP-450 Enzyme inhibitors (cimetidine, ketoconazole all azole **anti-fungal** are inhibitors) increase duration of action of metronidazole
- Inducers (phenytoin and phenobarbitone) decrease duration of action of metronidazole.
- Metronidazole inhibits **CYP-450 (2C9 & 3A4**) so :
  - increases anticoagulant effect of warfarin.
  - Increases lithium toxicity.

C.I. / PRECAUTIONS

metroNIDazole= babies NEED their mother's milk

- Pregnancy (especially in the 1st trimester) and breast feeding women.
- Alcohol intake — Drunk people shouldn't drive, they should ride the metro
- CNS diseases like epilepsy because of its Neurotoxicological effect
- Severe renal disease
- Severe hepatic disease

Drug: Tinidazole

M.O.A

Tinidazole has similar activity to metronidazole but better potency.

Pharmacokinetics

Advantages of tinidazole :

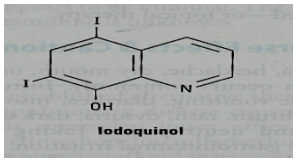
- has **longer** duration of action (12-14h) يستخدم بمرات أقل
- a **simpler** dosing regimen more potent.
- **a better** toxicity profile than metronidazole

Tissue or systemic Amebicides

Drug	Emetine and dehydroemetine Dehydroemetine better than Emetine	Chloroquine
Mechanism of action	• Emetine is an alkaloid derived from ipeca it is a plant which was used in the past to induce vomiting in people who takes overdose of tablet of drugs to attempt to suicide • while dehydroemetine is a synthetic analog. • Both are effective against tissue trophozoites of E.histolytica causing irreversible block of protein synthesis. • Because of major toxicity concerns **they have been almost completely replaced by metronidazole,** so we don't use them until if we really need them such as resistance for Metronidazole	Anti-malarial drug
Pharmacokinetics	• Have erratic oral absorption. the dose may or may not give the effect يعني ممكن يصير عندي تأثير للدوا وممكن لا • Given preferably subcutaneously but could be given by IM, **NEVER I.V** (bc of CVS toxicity) • Has long plasma half life about 5 days. The excretion will be difficult إلي متي ؟ مطول يعني !)emetine(• Metabolized & excreted slowly via kidney so they have a cumulative effect (stay in the blood for long time) • Should not be used for more than 10 days (usually 3-5 days) bc their T1\2 is long & excreted slowly, therefore they will be accumulated if used for a long time. • Dehydroemetine is less toxic than emetine	Queen still alive!
Clinical Uses	• Intestinal wall infections. • Amoebic liver abscess. • Severe forms of amebiasis **acute amoebic dysentery**, dehydroemetine is preferable due to less toxicity (3-5 days).	Used in combination with metronidazole or dehydroemetine for amebic liver diseases why only liver? Bc they are concentrated in the liver.
ADRs	**Serious toxicities**: cardiotoxicity Due to long half life, should not be given أي مات بسبب التسمم **GIT**: nausea, vomiting, diarrhea. Hypotension, cardiac arrhythmias, heart failure ⚠ Caution: the drug should not be used in patients with cardiac or renal disease, **in young children, or in pregnancy** teratogenic effect.	Hemolysis in G6PD deficient patients if I give it to patient with G6PD deficiency It will cause hemolytic anemia Pruritus is common Blurring of vision Remember from the neuropsychiatry block, they were depositing in the eye. Nausea, vomiting, abdominal pain, anorexia.

Luminal amoebicides amoebicides = with

Asymptomatic (carrier) -to eradicate cysts-

Drug	Diloxanide furoate	Iodoquinol
Action/M.O.A	• Mechanism of action is unknown • Direct amoebicidal action against luminal forms cyst • Not active against trophozoites in intestinal wall or extra-intestinal tissues.	• Mechanism of action is unknown • effective against the luminal forms of amebiasis it has iodine which gives ADRs 
Pharmacokinetics	• Ester of diloxanide + furoic acid . • Given orally. • It splits in the intestine liberating diloxanide • The unabsorbed diloxanide is the amoebicidal agent . • The absorbed portion (furoic acid or furoate) is excreted in urine .	• Is given orally • Poorly absorbed, excreted in feces.
Indications	• Drug of choice for asymptomatic intestinal infection (cysts passers). • to eradicate cysts of E.histolytica after treatment of invasive disease with systemic amebicides	• Luminal amoebicide for asymptomatic amebiasis.
ADRs	Flatulence Nausea, vomiting, abdominal cramps. Because it is absorbed only in the GIT the ADRs will be related ONLY for GIT	**GIT**: Nausea, vomiting, diarrhea. **Peripheral neuropathy** including optic neuritis with high dose Enlargement of the thyroid gland because of the present of iodine Iodine sensitivity. Interference with thyroid function tests (increase protein-bound serum iodine, decrease in measured (^{131}I* uptake). When the patient use Iodoquinol, It will do similar effect of ^{131}I* in the test will give false measurements. *it is an I (i) letter, not L (l)
Contraindications	• Pregnancy • Children (less than 2 years).	• Iodoquinol should be used with caution in patients with optic neuropathy, or thyroid disease. • **Discontinued** if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever).

Luminal amoebicides

Drug	**Paromomycin Sulphate**
Action/M.O.A	• Aminoglycoside antibiotic • Direct amebicidal action: causes leakage by its action on cell membrane of parasite. • Indirect effect: killing of bacterial flora essential for proliferation of pathogenic amoebae نتخيل البكتيريا والأميبيا برموا (promo) اتفاقية شراكة
Pharmacokinetics	• Given orally • Not significantly absorbed from GIT • Effective only against luminal forms of ameba • Small amount absorbed is excreted unchanged in urine (may accumulate with renal insufficiency).
Uses	Use in chronic amebiasis (carrier) to eliminate cysts (in cysts passers).
ADRs	Gastrointestinal distress and diarrhea. Remember that aminoglycosides may cause nephrotoxicity and ototoxicity!
C.I.	• Severe renal disease • patients with GIT ulceration

Summary for treatment of amebiasis

Asymptomatic dysentery (**cyst carriers**) The doctor will detect it when he do a stool analysis and find cysts, but the patient doesn't have any symptoms	**Luminal amebicides** Diloxanide or iodoquinol or Paromomycin
Amebic colitis and dysentery ameboma, and extra-intestinal disease	Metronidazole or tinidazole followed by luminal amebicides 1st choice
Hepatic abscess	Metronidazole or tinidazole or choroquine or dehydroemetine

Bacillary dysentery

Bacillary dysentery is Treated by:

Beta-lactams: Ampicillin, amoxicillin, third-generation cephalosporins (cefixime, ceftriaxone)

Cotrimoxazole (trimethoprim-sulfamethoxazole) (TMP-SMX) commonly used in traveller's diarrhea. Sulfamethoxazole prevent formation of dihydrofolic Trimethoprim prevent formation of tetrahydrofolic

Fluoroquinolones such as ciprofloxacin, ofloxacin

Macrolides: Azithromycin

Antimicrobial therapy is typically administered for 5 days.

Resistance to ampicillin, amoxicillin and sulfonamides, has been reported worldwide, and these agents are not recommended as empirical therapy.
Fluoroquinolones are first-line treatment for **shigellosis**.
Second line therapy include third generation cephalosporins pregnant women or children or breast feeding women →use cephalosporins Not Fluoroquinolones!

Until the culture results come in dysentery caused by infection, give empiric therapy in → combination of anti-protozoal + antibiotic.

Bacillary dysentery treatment

Drug	**Ciprofloxacin**
M.O.A	• Fluoroquinolones are first-line treatment for shigellosis. • Active against a variety of gram-positive and gram-negative bacteria. • block bacterial DNA synthesis and growth (DNA gyrase &topoisomerases).
Indications	• Bacterial diarrhea caused by shigella, salmonella and E coli. • Urinary tract infections • Respiratory tract infections • Soft tissues, bones, and joint infections
ADRs	Arthropathy (damage of growing cartilage). Especially in children so Here we should use Cephalosporins Phototoxicity GIT disorders (nausea, vomiting, diarrhea). CNS disorders (headache, dizziness). CVS disorder (prolonged QT interval). Liver toxicity. نتخيل إننا نقول لأطفال متحمسين بالسوبر ماركت "اصبروا(cipro) تجي عربية التسوق(t) " from these ADRs you can know what are the contraindications
Contraindications	• Children, pregnancy, nursing mother. I should use Cephalosporins instead • Epilepsy • Arrhythmias. • Should not be combined with antacids, divalent cations it will decrease the effect of the drug
Drug	**Cephalosporins (**cefixime , ceftriaxone)
M.O.A	• They are 3rd generation cephalosporin. It acts with children • Act by interfering with synthesis of peptidoglycan, a major structural component of bacterial cell wall.
P.K	Oral cefixime or parenetral ceftriaxone are safe and effective.
uses	In case of children or patient allergic to sulfonamides, cephalosporins or azithromycin may be used (note that sulfonamides are also C.I with preg. & child)

SUMMARY

This summary was included in doctor's slides

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- Maintain fluid intake (oral rehydration therapy or Intravenous fluid therapy).
- Asymptomatic luminal amebiasis is treated by luminal amebicides (diloxanide, or iodoquinol or paromomycin).
- Metronidazole is the mainstay of therapy for invasive amebiasis (followed by luminal amebicides to prevent relapse).
- Chloroquine has also been used for patients with hepatic amebiasis.
- Dehydroemetine is useful but not preferable due to CVS toxicity
- Ciprofloxacin is the drug of choice in bacillary dysentery In children and pregnancy, ceftriaxone or cefixime is the choice.

The summary of all drugs that were mentioned in the lecture is on the next tow slides

systemic amebicides

Drugs	Action /Mechanism	Indications	ADRS	C.I	Notes
Metronidazole	treating invasive amebic infections (intestinal & extra-intestinal amebiasis). should be followed by luminal amebicides. Mechanism: inhibits DNA replication. Does not eradicate cysts from intestine	Extra-luminal amoebiasis: is the drug of choice Giardiasis Peptic ulcer Pseudo-membranous colitis anaerobic bacterial in dentil practice	metallic taste Oral Thrush Dysuria, dark urine Disulfiram-like effect if taken with alcohol Neurotoxicological effect Convulsion	C.I: Pregnancy and breast-feeding women. Alcohol intake CNS diseases Severe renal disease Severe hepatic disease	Drug Interactions: increases anticoagulant effect of warfarin. Increases lithium toxicity. Tinidazole is the better drug (more potency).
Tinidazole					
Emetine, dehydroemetine	Mechanism: effective against tissue trophozoites of E. histolytica causing irreversible block of protein synthesis.	Amoebic liver abscess. Intestinal wall infections. Severe forms of amebiasis **acute amoebic dysentery**	Serous Cardiotoxicity: Hypotension, cardiac arrhythmias, heart failure should not be used in patients with cardiac or renal disease, in young children, or in pregnancy.		dehydroemetine is preferable due to less toxicity
Chloroquine	combination with metronidazole or dehydroemetine for amebic liver diseases		Hemolysis in G6PD deficient patients. Pruritus Blurring of vision.		

	Drugs	Action/ Mechanism	Indications	ADRS	C.I	Notes
Luminal Amebicides	Diloxanide furoate	Action: The little unabsorbed diloxanide is the amoebicidal agent . Mechanism: Unknown	1st choice for asymptomatic intestinal infection (cysts passers). to eradicate cysts To eradicate cysts after tissue amebicides treatment	Flatulence	Pregnancy Children (less than 2 years).	Direct amoebicidal action against luminal forms Not active against trophozoites in intestinal wall or extra-intestinal tissues.
	Iodoquinol	effective against the luminal forms of amebiasis Mechanism: Unknown	Luminal amoebicide for asymptomatic amebiasis	Peripheral neuropathy Enlargement of the thyroid gland.	optic neuropathy , or thyroid disease.	discontinued if it produces persistent diarrhea or signs of iodine toxicity
	Paromomycin Sulphate	Direct effect: amoebicidal action (causes leakage by its action on cell membrane of parasite). Indirect effect: killing of bacterial flora essential for proliferation of pathogenic amoebae.	chronic amebiasis to eliminate cysts	Gastrointestinal distress and diarrhea nephrotoxicity and ototoxicity	Severe renal disease patients with GIT ulceration	
Bacillary Dysentery	Ciprofloxacin	block bacterial DNA synthesis and growth (DNA gyrase &topoisomerases).	Bacterial diarrhea (caused by shigella, salmonella and E coli).	Phototoxicity Arthropathy (damage of growing cartilage).	Children, preg.& nursing mother. Epilepsy Arrhythmias Should not be combined with antacids, divalent cations.	Cotrimoxazole in traveler's diarrhea.
	Ceftriaxone & cefixime	Act by inhibiting cell wall synthesis (interfering with synthesis of peptidoglycan)	Indications: In case of children or patient allergic to sulfonamides, cephalosporins can be used.			

MCQ

Q1: 26 years old male who came to the hospital for routine test with no symptoms or diarrhea, the stool analyze was done also. Which shown that he has many cysts of Entameba Histolytica. Which one of the following anti amoebic drug can be used in his case?

A- Metronidazole B- Diloxanide furoate C- Iodoquinol

Q2: Patient who has liver abscess due to intestinal amoebiasis was treating with metronidazole for 5 days. After he complete his treatment, which one of the following anti amoebic drug can be used as second treatment in next stage?

A- Metronidazole B- Diloxanide furoate C- Iodoquinol

Q3 : Epileptic Patient with intestinal amoebiasis, which one of the following anti amoebic drug is contraindicated in his case ?

A- Metronidazole B- Emetine C- Iodoquinol

Q4: A 53 years old male who is a chronic alcoholic, present to the ER with flushing, tachycardia, nausea and vomiting. His medical history shows that he started the symptoms after taking anti amoebic drug to treat his bloody diarrhea. Which of the following drug is most likely to cause these symptoms?

A. Metronidazole B. Iodoquinol C. Chloroquine

Q5: Which one of the following anti amoebic drug can not be used if we have patient with cardiac disease ?

A- Metronidazole B- Emetine C- Iodoquinol

Q6: Which one of the following can not be used in patient with hemolytic anemia due to genetic defect in glucose phosphate dehydrogenase in his RBCs?

A. Metronidazole B. Iodoquinol C. Chloroquine

1. B
2. B
3. A
4. A
5. B
6. C

MCQ

Q7: Which one of the following anti amoebic drug is the best for cyst passers eradication of Entameba Histolytica ?

A- Metronidazole B- Diloxanide furoate C- Iodoquinol

Q8: Emetine is now used only as a reserve drug for amoebiasis in compare with metronidazole because :

A- It produces a slower response.
B- It has more cardiotoxic potential.
C- It is less effective in extra-intestinal amoebiasis

Q9: Which one of the following anti amoebic drug may give a false result for thyroid function test ?

A. Metronidazole B. Iodoquinol C. Paromomycin Sulphate

Q10: Which one of the following drug can be act as antibacterial and antiprotozoal ?

A. Metronidazole B. Iodoquinol C. Paromomycin Sulphate

Q11: 8 years old child who has dysentery diarrhea caused by shigella. Which one of the following antibiotic can not be used in his case ?

A. Ciprofloxacin B. Ceftriaxone C. amoxicillin

Q12: 8 years old child who has dysentery diarrhea caused by shigella. Which one of the following antibiotic can be safe to be used in his case ?

A. Ciprofloxacin B. Ceftriaxone C. tetracycline

7. B
8. B
9. B
10. C
11. A
12. B

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قادة فريق علم الأدوية :

- جومانا القحطاني - اللولو الصليهم

- فارس النفيسة

الشكر موصول لأعضاء الفريق المتميزين :

روان القحطاني

وجدان الزيد

رحاب العنزي

شذا الغيهب

عبدالرحمن الراشد

عبدالكريم الحربي

References :

1- 436 doctors slides and notes
2- 435 teamwork

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* الشعار و القالب الأساسي من تصميم لين التميمي