Eukaryotics and Antieukaryotics

Fungi and Antifungals
Protozoans and Antiprotozoals
Helminthes and Antihelminthics
MYCOLOGY

Mycology Check List for the Exam

1. Coccidioides
2. Candida
3. Cryptococcus
4. Histoplasma
5. Aspergillus
6. Blastomyces
7. Sporothrix

C3HABS!

During the third week of an expedition a desert in New Mexico, one of the campers is presented with malaise, fever, myalgia, arthralgia, and dyspnea. On examination there were red spotty rashes similar to measles on his knees and ankles. The chest x-ray is pleural effusions in both lungs in addition to presence of multiple thin-walled cavities. The most likely diagnosis is:

(A) An infection caused by Mycobacterium marinum
(B) An infection caused by Mycoplasma pneumoniae
(C) Blastomycosis
(D) Coccidioidomycosis
(E) Histoplasmosis

Treatment of Choice for this patient would be:

(A) Amphotericin B
(B) Griseofulvin
(C) Nystatin
(D) Tetracycline
(E) Thiabendazole

Answer key

- Coccidioides immitis: Dwells in arid regions; it is highly endemic to southwestern USA and northern Mexico. Infections follow inhalation of the arthrospores.
- Treatment: [A] **COKE!**
- Blastomyces dermatitidis: Endemic to North America
- Histoplasma capsulatum: Central and Mid-eastern USA; associated with bird and bat feces.
- Mycoplasma pneumoniae: Needs a dense crowd to spread out (i.e. to spread walking pneumonia). Common in temperate climates and among school children.

About Coccidioidomycosis

“Nothing makes more sense than a cold can of Coke in the middle of a hot desert!”
Paracoccidioidomycosis is a systemic chronic granulomatous mycosis mostly seen in Brazil and South America. Unlike most other systemic mycoses, it affects immune-competent patients as well. It often starts as a primary pulmonary infection and then disseminates and forms painful ulcerative granulomatas of buccal, nasal and gastrointestinal tract. Interestingly, it almost never causes infections in women during childbearing ages. Which of the following fungi is closely related to paracoccidioides?

A. Blastomycosis  
B. Coccidioidomycosis  
C. Cryptococcus  
D. Histoplasma  
E. Aspergillus

What is the most commonly asked question about blastomycosis on the exam?

- You can spot me almost anywhere!
- 20 million women with vaginal infection know me quite well. Majority of them get introduced to me while working with three groups of my allies; antibiotics, steroids and contraceptives!
- If I get into the mouth, I will make white creamy exudative patches!
- I am expert at causing diaper rash in infants, and I love traveling and disseminating into all organs of my AIDS victims!
- I love brewed Budweiser! That’s why they call me “budding yeast”!
- I love to spread myself under the body heat! Those who catch me taking a body-heat tan like to say that “I am pseudo-hyphenating on their bodies!”
- What I mostly hate are three exterminators: Amphoterrible, Ketoconazole and Fluconazole!
- We can all make it together to awesome scores on the USMLE and COMLEX, if you tell me who I am!

Answers

- The most commonly asked question about blastomycosis on the exam is osteomyelitis (North American Osteoarticular Blastomycosis). It occurs in 30% of patients with disseminated Blastomycosis. It affects spine, long bones and ribs. It may also spread to joints (knee, elbow and ankle). Seen mostly in the elderly farmers and hunters.

- “Who am I?” = Candida albicans
- The correct answer to multiple choice question is [A] blastomycoses. AKA. Brazilian Blastomycosis, South American Blastomycosis, and Paracoccidioidal granuloma. Lack of the disease in women is most likely estrogen-related. Treatment: includes sulfonamides sulfadimethoxime, sulfadiazine). Amphotericin B is the second-line choice.
# Fungal Diseases

<table>
<thead>
<tr>
<th>Fungal Disease</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Coccidioidomycosis** | - Coccidioides immitis  
- Arid regions; Southwestern USA and Mexico  
- Pulmonary symptoms; Amphotericin B or ketoconazole |
| **Histoplasmosis** | - Histoplasma capsulatum; Ohio River Valley and Mississippi area  
- Acute or chronic pulmonary symptoms  
- AIDS (disseminated type) |
| **Blastomycosis** | - North American blastomycosis (South-east USA); Self-limited pneumonia. Osteomyelitis, pneumonia and dermatitis.  
- Related south American type: Paracoccidioides brasiliensis (soil and rotten wood) |
| **Aspergillosis** | - Confined to lung; associated with AIDS and TB.  
- Most common form is A. fumigatus  
- Treatment: Amphotericin B |
| **Sporothrix** | - Sporothrix schenckii; Seen in florists and gardeners  
- Grows on Sabouraud's agar. Clinical presentation is similar to Mycoplasma marinum  
- Most common form is lymphangitic (spread along lymph vessels).  
- Treatment: Amphotericin B |
| **Cryptococcosis** | - Cryptococcus neoformans; associated with AIDS and long-term use of glucocorticoids  
- Meningoencephalitis, skin and pulmonary infections  
- India Ink staining of CSF |
| **Candidiasis** | - Commensals of mouth and vagina (Oropharyngeal thrush)  
- Associated with broad spectrum antibiotic therapy, diabetes, AIDS  
- Treatment: Fluconazole, ketoconazole and amphotericin B |
| **Dermatophytes** | - Two major genera are Trichophyton (more common) and Microsporum. Tinea corporis (Ring Worm)  
- T. cruris (Jock Itch); T. pedis (Athlete’s foot); T. capitis (head)  
- Diagnosis: Skin scrapings fluoresce with wood’s ultraviolet light (diagnostic of Microsporum)  
- Treatment: Topical imidazoles (e.g. miconazole) |
Mini Pre-test Question Set

1. A 15-year-old boy presents with a few lesions on the inner side of his arm. The lesions are red and ring-shaped with relatively raised borders and central clearings. The edge of the rash appears elevated and is scaly to the touch (see the exhibit). The patient claims that the ring of his lesions appeared several days ago and has been expanding since then. The patient is treated with topical clotrimazole and his lesions disappear after a few days. What was the most likely diagnosis?

   A. Tinea pedis
   B. Tinea unguium
   C. Tinea capitis
   D. Tinea cruris
   E. Tinea corporis

2. Your patient is an 11-year-old boy with scaly patches on his scalp (see the exhibit). Based on your clinical suspicion, a sample of affected hair is viewed under the Wood’s lamp. The sample fluoresces under the lamp. What is the most likely diagnosis and the causative agent?

   A. Tinea capitis due to Microsporum
   B. Tinea capitis due to Trichophyton
   C. Tinea corporis due to Microsporum
   D. Tinea corporis due to Trichophyton
   E. It could be any of the above

3. Management of which of the following two fungal infections requires oral administration of antifungal medications?

   A. Tinea pedis and capitis
   B. Tinea pedis and cruris
   C. Tinea unguium and capitis
   D. Tinea cruris and corporis
   E. Tinea pedis and candidiasis

4. Your patient is 16-year-old female with a history of asthma. She complains of painless whitish patches in her mouth and on her tongue, and she claims that for the most part they are brushed off by scrubbing with a toothbrush. She also claims that occasionally she has difficulty with swallowing. Her history is significant for asthma. Currently, she takes inhalers that contain beta-2 agonists and glucocorticosteroids. What is your most likely diagnosis?

   Diagnosis: ________________________________

5. What are at risk populations for oral thrush?

6. What form of candidiasis is not uncommon in pregnant women who undergo treatment with broad spectrum antibiotics?

7. What are treatments for Candida?

   _______________________________________
   _______________________________________

Answers and Explanations (pretest 1-4)

Question 1
- [E]. Tinea corporis (A.K.A. ringworm) is a superficial fungal infection (dermatophytosis) due to Trichophyton mentagrophytes.
- It affects arms, legs, and glabrous (hairless) skin; however, it may occur on any part of the body (corpus = body!). Enlarged raised red rings with a central area of clearing (hence, ringworm).
- Treatment: Topical antifungals such as clotrimazole, ketoconazole, and miconazole

Must-Know Associations
- Tinea pedis (athlete’s foot) mostly between the toes.
- Tinea unguium (onychomycosis) under the nails (unguis = nail).
- Tinea capitis, on the scalp and is also highly contagious.
- Tinea cruris, (jock itch), mostly happens in obese males and in the crural folds of the inner and upper thigh.

5. Northwestern Medical Review
Question 2
- [A]. Tinea capitis due to Microsporum.
- The top two causes of fungal infections are due to Trichophyton (the most common) and Microsporum.
- If a fungal hair sample fluoresces under the Wood's (black) lamp it is due to Microsporum; if not, it is due to Trichophyton.
- Mnemonic: You turn the “M” of Microsporum upside-down to make the “W” of Woods!
- Tinea capitis (A.K.A. Ringworm of the hair or scalp)
- Causes: Trichophyton and Microsporum genera
- Findings: Multiple patches of hair loss that may be accompanied by inflammation, scaling, pustules, and itching.
- Predominantly seen in pre-pubertal children
- At times the host’s response may cause formation of granulomatous kerions that may be accompanied by secondary bacterial infections. It usually presents itself as raised, spongy lesions.
- Kerions are severely painful inflammatory and deep suppurative lesions that may often resolve spontaneously. Oral Griseofulvin is the treatment of choice for kerions.

Question 3
- [C]. Management of Tinea capitis (scalp ringworm) and T. unguium (onycomycosis) must be done by oral administration of Griseofulvin.
- All others should be treated topically with medications such as clotrimazole and miconazole.

Question 4: Oral candidiasis (oral thrush)

Question 5: HIV-positive and AIDs patients; Immune-suppressed individuals; Diabetics; Patients with the history of long-term glucocorticoid therapy; Young children

Question 6: Vulvovaginitis due to Candida!

Question 7:
- Topical: Fluconazole, ketoconazole
- Oral: Nystatin or ketoconazole for swish and swallow use
- Systemic (AIDs): Amphotericin B

Checklist of Antifungals
1. Amphotericin B
2. Flucytosine
3. Ketoconazole, Fluconazole, Clotrimazole, and Miconazole
4. Nystatin
5. Griseofulvin

Amphotericin B
- A polyene macrolides
- Binds to unique fungal cell component ergosterol and produces pores in fungal cells. It causes death of the fungus due to Na+ and K+ leakage
- Ergosterol is similar to cholesterol.
- Amphotericin has a very low affinity for cholesterol. Hence, causes selective toxicity in fungi only.
- No antibacterial activity
- Fungicidal
- Does not pass through blood-brain barrier.
- Must be applied intra-thecally for meningitis. For all other infections it is used IV.
- Used for systemic fungal infections
- Indications of Amphotericin B
  - Cryptococcus
  - Blastomyces
  - Coccidioides
  - Histoplasma
  - Candida
  - Aspergillus
Side-effects of amphotericin: Febrile state (chills, hypotension and tachypnea), nephrotoxicity and neurotoxicity

Other must-know polyene antimycotics: Nystatin and Rimocidin

Flucytosine
- Pyrimidine analogue (similar to 5-fluorouracil anticancer drug)
- Used in conjunction with amphotericin B
- Mechanism: First it is converted to fluorouracil. The latter inhibits thymidilate synthetase and fungal DNA/RNA synthesis.
- Oral administration
- Main Advantage: Better CNS and CSF penetration than Amphotericin.

A 30-year-old male AIDS patient is admitted to the hospital with fever, nausea, and vomiting. CSF examination indicates lymphocytosis, decreased concentration of glucose and increased protein. India ink staining of the CSF shows cells with a halo surrounding them. What is the most probable diagnosis?

Most fungi are or will become resistant to Flucytosine very quickly. As such Flucytosine therapy must be accompanied by other antifungals. Which two fungi are not usually resistant to Flucytosine?

The patient (in the above case) was not presented with headache, alteration of mental status and nuchal rigidity. Why?

In which two human populations are manifestations of meningitis are similar to AIDS?

Answers
- Diagnosis: Cryptococcus neoformans
- Concomitant medication: Amphotericin

Candida and Cryptococcus!
Meningeal inflammatory reactions require efficiency and potency of immune system. AIDS patients lack a patent immune system!
Elderly and very young children: They lack of full immunologic potentials!
About Kernig’s and Brudzinski’s Signs
- Clinical Signs of meningitis
- Due to nuchal (neck) rigidity/stiffness
- In Kernig’s, upon raising the Knee, the patient moves his/her head forward. In Brudzinski’s, upon bending the neck, the patient raises his/her knee.
- Other symptoms of meningitis are: Headache and alteration of mental status.

About Micafungin
- An IV medication that inhibits the production of beta-1,3-glucan, an essential component of fungal cell walls.
- Indicated for the treatment of candidemia, acute disseminated candidiasis and Candida abscesses.
- It is also used for the prophylaxis of Candida infections in patients undergoing stem cell transplantation
- Other use: Systemic aspergillus infections
- Mechanism of fungal resistance: Alterations in the active site of beta-glucan synthase

What class of antifungals is known as “penicillins of antifungals”?

**Name four drugs that disrupt mitosis by disturbing spindle fibers:**

1. V
2. P
3. C
4. G

AZOLE DRUGS
- Fluconazole, Ketoconazole, Clotrimazole, Miconazole
- Inhibit fungal ergosterol biosynthesis. Inhibit fungal ergosterol biosynthesis by inhibiting lanosterol demethylase that is a key enzyme in ergosterol synthesis.
- All azoles can be used orally

**Ketoconazole**
- Oral administration only
- Requires low pH for function. Avoid antacids.
- Inhibits P450
- Blastomyces, Coccidioides, Histoplasma, and Candida
- Also for hypercortisolism (due to its inhibitory effect on human steroids).

**Drugs that Disrupt Mitotic Spindle Function**
- Vinblastine and vincristine (anticancer, make unstable microtubules)
- Paclitaxel (anticancer, makes stable microtubules)
- Colchicine (anti-inflammatory, stops neutrophil migration)
- Griseofulvin

**Must-Know Teratogenic Drugs**
- Alcohol
- Captopril
- Retinoic acid (isotretinoin)
- Diethylstilbestrol
- Warfarin
- Lithium
- Methotrexate, Methimazole (and PTU), Metronidazole (Questionable)
- Tetracycline
- Valproic acid, Phenytoin and Carbamazepine
- Griseofulvin

**Griseofulvin**
- Binds to and deposits in keratinized tissues--skins, nail, and hair
- Disrupts mitotic spindles
- Fungastatic
- Low water solubility
- Metabolized by the liver, and stimulates P-450
- Duration of action after oral administration is very long (months)
- Used orally for dermatophytes (Tinea, and Ringworm)
- Side-effects:
  - Teratogenic and carcinogenic
  - Increase coumadin metabolism via P-450

*Greasy food and skin for Griseofulvin! It is administered orally and is used for dermatophytes!*

**Answer:** Penicillins of Antifungals
- Echinocandins (e.g. micafungin and caspofungin)
- Reason: Inhibit synthesis of glucan in fungal cell wall.
- Mechanism of action: Noncompetitive inhibition of the enzyme 1,3-beta glucan synthase
Fluconazole

- Oral or IV
- Better CNS penetration. In contrast to Ketoconazole it is not affected by low pH
- Indications
- Cryptococcal meningitis in AIDS
- Candida
- Adverse Reactions
  - Steroid inhibition.
  - Gynecomastia
  - Liver dysfunction due to P-450 inhibition that will distort liver' ability to metabolize medications

Although azole drugs can be used orally, all but two cause serious side effects that restrict their oral application. Which two azoles are predominantly used orally?

______________________________ and _________________

What is the main difference between oral administration of Ketoconazole and Fluconazole?

______________________________

Of the two azoles, Ketoconazole and Fluconazole, only one can readily penetrate the CSF. Which one is it?

______________________________

Which of the two is more suitable for treatment of fungal meningitis caused by Coccidioides and Cryptococcus--Ketoconazole or Fluconazole?

______________________________

Answers:
- Ketoconazole requires low pH
- Fluconazole enter the CSF!
- Fluconazole for fungal meningitis caused by Coccidioides and Cryptococcus

A male kidney transplant patient who has been on a particular immune suppressive medication contracts candidiasis. For treatment of his fungal disease, ketoconazole therapy is initiated. Later, the patient presents with nephrotoxicity and lymphoma. It is determined that these symptoms are due to the immune suppressant medication that he was taking. What is the most likely immune suppressive medication?

C______________________________! Binds to cyclophilin of lymphocytes--especially T cells, and blocks IL-2 and IL-4 formation!
Toxicity predisposes to viral infections, lymphoma and nephrotoxicity.

Inhibition of P-450 by Ketoconazole potentiates toxicities of several concomitant medications. Name 5 drugs that are commonly potentiated by this mechanism?

C______________________________ (Immune Suppressant)
P______________________________ (Class IB Antiarrhythmlic and Anticonvulsant)
T______________________________ (H1 Histamine Antagonist)
S______________________________ (Anti-hyperglycemic)
W______________________________ (Anticoagulant)

Nystatin

- Functionally similar to amphotericin B (a polyene macrolide)
- Acts via ergosterol interruption
- It cannot pass through the GI mucosa
- Only topical application
- Used for oral and esophageal candidiasis as an oral agent (Swish and swallow agent).

Answer:
- Cyclosporine (immune suppressant)
- Phenytoin (IB Antiarrhythmlic and Anticonvulsant)
- Terfenadine (H1 Histamine antagonist/allergic rhinitis)
- Sulfonylurea (anti-hyperglycemic )
- Warfarin (anticoagulant)
Drugs that Inhibit P450

- Phenylbutazone
- Phenytoin
- Erythromycin
- Chloramphenicol
- Cimetidine
- Cyclosporine
- Ciprofloxacin
- Ketoconazole
- Sulfonylureas
- Grapefruit

A 55-year-old diabetic patient has total cholesterol level of 270 mg/dL and HDL of 30 mg/dL. He receives a prescription for pravastatin and he is advised not to eat grapefruit with his medication. Why consumption of grapefruit is contraindicated with pravastatin?

- Statins are metabolized by CYP 3A4 in the liver
- Grapefruit has furanocoumarin that competitively inhibits CYP 3A4

Causes of Drug-induced Gynecomastia

- Alcohol
- Spironolactone
- Cimetidine
- Flutamide (antiandrogen)
- Finasteride (5-alpha reductase inhibitor)
- Fluconazole and Ketoconazole

Although all azoles can be used orally, all but two cause serious side-effects that restrict their oral application. Which two azoles are predominantly used orally?

The two azoles are ketoconazole and fluconazole.

Antifungals Acting on Ergosterol

- Amphotericin B and Nystatin bind to ergosterol and make holes in fungal membrane
- Ketoconazole inhibits ergosterol synthesis by inhibiting lanosterol demethylase

Mechanisms of Resistance to Antifungals

<table>
<thead>
<tr>
<th>Antifungals</th>
<th>Azoles</th>
<th>Echinocandins</th>
<th>Polyene macrolides</th>
<th>Pyrimidine analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>Miconafungin and Caspofungin</td>
<td>Amphotericin B and Nystatin</td>
<td>Flucytosine</td>
</tr>
<tr>
<td></td>
<td>Changing structure of lanosterol demethylase</td>
<td>Changing active site of 1,3-beta-glucan synthase</td>
<td>Changing membrane lipid’s structure</td>
<td>Changing structure of DNA polymerase</td>
</tr>
</tbody>
</table>
DRILL QUESTIONS

1. What is the medication of choice for Athlete’s Foot (Tinea pedis)?

   ____________________________________________

2. What cause of meningitis is characteristically stained with India ink due to its capsule?

   ____________________________________________

3. What is the most common source of Cryptococcus neoformans?

   ____________________________________________

4. What fungal disease is characteristically associated with eosinophilia?

   ____________________________________________

5. What fungal disease is notorious for causing osteomyelitis?

   ____________________________________________

6. What is the most common animal vector of histoplasmosis?

   ____________________________________________

7. What is the most common means of acquiring Sporothrix infection?

   ____________________________________________

8. Clinical picture of what disease is similar to Sporothrix schenckii infection?

   ____________________________________________

9. What 3 antifungals are only used topically?

   ____________________________________________

10. A 22-year-old male college athlete has been treated with miconazole for recurring itching and burning sensation between his toes on several occasions within the past 24 months. He is now admitted with the complaint that he has been taking the medication within the past two weeks with no apparent improvements in his condition. Assuming that the causative organism has become resistant to the medication, which of the following options better explains the mechanism of the resistance?

    A. Alteration in the structure of lanosterol demethylase
    B. Alteration in the active site of 1,3-beta-glucan synthase
    C. Change in membrane lipid structure
    D. Change of metabolism from aerobic to anaerobic mode
    E. Change in the structure of the DNA polymerase

    8. Mycobacterium marinum
    7. Rose thorn finger prick
    6. Bats and bat droppings
    5. Blastomycosis
    4. Aspergillosis
    3. Pigeon droppings
    2. Cryptococcus
    1. Miconazole
# Protozoan Parasites

## Giardiasis (G. lamblia)
- Drinking untreated water. Beavers!
- Persistent non-bloody diarrhea; steatorrhea; and no fever
- Owl-eyed trophozoites
- Poor fecal hygiene: day-cares; homosexuals; associated with selective IgA deficiency
- Metronidazole

## Malaria
- Plasmodium falciparum (black water fever) and vivax
- Anopheles mosquitoes
- Periodic bouts of fever every 48 hours when the plasmodia lyse the red cells. The only plasmodium with 72-hours pattern is P. malariae
- Chloroquine, Quinine and Pyrimethamine

## Trichomoniasis
- Trichomonas vaginalis (seen in; 25% of sexually active females)
- Flagellated and undulating membrane
- Persistent vaginitis; Odiferous frothy discharges. Asymptomatic males
- Metronidazole

## Toxoplasmosis
- Toxoplasma gondii; Cats (also sheep and pigs)
- Cysts in uncooked pork
- Transplacental transmission; lymphadenopathy, encephalitis, ocular infection; AIDS!
- Pyrimethamine and Sulfadiazine

## Amebiasis
- 3rd worldwide leading fatal parasitic disease
- Entamoeba histolytica Reservoir is human GI
- Diarrhea and heme-positive stool; invasion of submucosal and portal circulation, and amebic liver abscesses
- Diagnosis: Flask-shaped ulcers and low PMNs in the stool
- Metronidazole

## Trypanosomiasis
- T. cruzi (Chagas or American Sleeping Sickness); reduviid bug (kissing bug); Nifurtimox (nitro-anion and superoxide radicals); Suramin (NADH-reduction inhibitor); and Pentamidine (distorts mitochondrial function)

## Leishmaniasis
- Sandfly!
- Invades reticuloendothelial system; Middle East, South and Central America
- Manifestations: Cutaneous, Mucocutaneous, Visceral (Kala-azar)
- Sodium stibogluconate (inhibits glycolysis)

## Others
- Cryptosporidiosis. Milwaukee diarrhea. Immune-compromised.
The number 1 worldwide fatal infection is due to:

Malaria

- The three important causes of malaria are Plasmodium vivax, malariae and falciparum (most vicious)
- Transmitted by injection of sporozoites by the Anopheles mosquitoes

- Febrile paroxysms of chills and fever occur every 48 hours when merozoites lyse RBCs.
- Febrile paroxysms occur every 48 hours for all plasmodia except P. malariae (every 72 hours).
- “Black Water Fever” is the term used to describe the appearance of urine in Falciparum.
- Blood schizocidals clear erythrocytic plasmodium

ANTIMALARIALS

Chloroquine

- Selectively gets concentrated in the infected RBCs
- Acts on all intra red cell malarial parasites except Chloroquine-resistant Plasmodium falciparum
- One weekly oral dose
- Side Effects: Hemolytic anemia, retinal toxicity, and myocardial depression.

Mechanism of Chloroquine

- Plasmodium uses the globin of hemoglobin within its vacuoles (lysosomes) to derive its own proteins. It has no use for the heme part that is toxic. It converts heme to non-toxic crystals (hemozoin).
- Chloroquine enters the parasitic vacuole as uncharged molecule and becomes charged (with H+) in the acidic intra-vacuolar environment and gets trapped. It then makes a complex with heme that is toxic and causes lysis of the RBCs together with the parasites.

Pyrimethamine

- Inhibits dihydrofolate reductase (antifolate)—more selectively in parasites
- Often combined with sulfas for P. falciparum.
- With sulfadiazine for toxoplasmosis

Quinine

- Oral blood schizonticidal
- Used for chloroquine resistant species
- Rapid onset
- Mechanism of Quinine-Related Drugs: Form cytolytic complexes with Fe-protoporphyrin IX (heme) and accumulate in the food vacuoles of the parasite and kills the parasite and the host cells.
- Side Effects: Cinchonism and arrhythmias

Primaquine

- Tissue schizonticidal
- It is the choice drug for extra-erythrocytic forms—hepatic and gametocytic
- It also acts on blood phases
- Not effective for acute attacks
- Side Effects
  - Induction of hemolytic anemia in patients with glucose 6-P-dehydrogenase deficiency
  - Methemoglobinemia
  - Agranulocytosis
Life Cycle of Malaria and Associated Medications

1. Injected Sporozoites
2. Migration to Liver
3. Trophozoite formation in hepatocytes
4. Merozoite invasion of red cells
5. Merozoite multiplication and release
6. Invasion of new red cells, and re-multiplication of schizonts.
7. Some merozoites become gametocytes
8. Gametocytes are picked up by another biting female anopheles (source of spreading infection)

- Chloroquine
- Quinine
- Pyremethamine
- Primaquine

Symptoms of Cinchonism are tinnitus, slight deafness, photophobia, mental dullness, confusion and nausea.

Name the two drugs that are commonly associated with cinchonism:

Your clue is that they both start with letter “Q” and end in “ine”!

Q_______________________ine
Q_______________________ine

Both Cause CinQonism!

ANTIAMEOBICS

Metronidazole
- Entamoeba histolytica.
- Also effective for Gardnerella, Trichomonas, Bacteroides, Helicobacter and Clostridia.
- AKA. Flagyl. Because it kills flagellated organisms!
- Mechanism: After entry into the protozoa it is reduced by pyruvate ferredoxin oxidoreductase that normally produces ATP for the parasite. The reduced metronidazole captures (sinks) electrons and deprives the bug from energy and also facilitates accumulation of free radicals that are toxic to the bug.
- Adverse Reactions: GI upset and Disulfiram-like reaction with alcohol
Toxoplasma gondii
- Associated with AIDS and immunosuppressant therapy
- Cysts ingested by uncooked pork
- Cat (main host) feces is a major source of contamination (zoonotic disease)
- Symptoms: Lymphadenopathy, encephalitis (seizures, ataxia), and retinal infection (visual loss)
- A TORCH organism: Transplacental transmission
- Treatment: Sulfadiazine and Pyrimethamine

The most common cause of waterborne epidemics of gastroenteritis in the USA is: ________________

Pneumocystis Carinii
- Many individuals may harbor the organism with no apparent symptoms
- Associated with AIDS and immunosuppressant therapy
- PCP (Pneumocystis carinii pneumonia) is the most common opportunistic AIDS-associated infection
- Treatment: Trimethoprim and sulfamethoxazole

Trichomonas Vaginalis
- Flagellated and sexually transmitted
- Females: Frothy, malodorous vaginal discharge (males asymptomatic)
- Treatment: Metronidazole

Giardia lamblia
- Two forms: Motile/Flagellated (kite-like trophozoite) and cyst form
- 5% of US adults harbor Giardia asymptptomatically
- Outbreaks associated with sewage contaminated water and outdoor water (Beavers)
- Treatment: Metronidazole
What does this caricature picture remind you of?
Hint 1: It is NOT a frothy strawberry smoothie!
Hint 2: To make froth you have to stir the liquid!

Leishmaniasis
- Transmitted by sandfly
- Invades reticuloendothelial system
- Endemic to Middle East, South and Central America
- Different forms of disease: Cutaneous, Mucocutaneous, Visceral (Kala-azar)
- Treatment: Sodium stibogluconate (inhibits parasite’s glycolysis)

Answer to caricature picture:
- Trichomonas
- Vaginal discharges are pale, yellow-green, frothy, and malodorous.
- The cervix is red in color; “strawberry cervix” due to erythematous macular lesions on the surface of the cervix

Trichomonas swims in the secretions, stirs them up, and makes froth!

Trypanosomiasis
- T. Cruzi (Chagas or American Sleeping Sickness)
- Vector: Reduviid bug (kissing bug)
- Symptoms: Early symptoms are chancre at bite site, cardiomegaly and accelerated heartbeat, rash, fever. Later manifestations in addition to mega-esophagus and megacolon involve nervous system and includes mood changes sleepiness and eventual coma.
- Treatment
  - Nifurtimox (nitrofuran-related compound that produces nitro anions and oxygen radicals and breaks the parasite’s DNA)
  - Suramin (an NAD-reduction and metabolism inhibitor)
  - Pentamidine (binds to and distorts DNA/RNA synthesis in addition to affecting mitochondrial function)
  - Benznidazole: Induces formation of free radicals and electrophilic metabolites within the parasite

This famous bug is associated with an intense kissing urge in some women. It is inducible by introduction of the sensitized subjects to:

Answer: Please see further below

Common Chronic (Late) Symptoms of T. Cruzi
- Cardiomegaly: Sensitized subjects have a big heart for the bug! It is postulated that antibodies against the bug may react against the myocardium!
- Accelerated beats: Afflicted subjects can’t control their heartbeats after the bug kisses them (transfers the disease) Antibodies of host causes parasym pathetic dysfunction and over-stimulation of sympathetics (catecholamine-induced cardiomegaly)
- Sleepiness: After one close encounter with the bug the afflicted individuals like to sleep and romance the bug in their dreams!
- Mega-esophagus: Often the sight of the bug gives the afflicted women trouble with swallowing—food simply stays in their throats. Toxin destroys ganglion cells of GI wall!
- Megacolon: When bug is around, some afflicted women don’t even go to bathroom (they want to see the bug so badly that they postpone using the bathroom!) Toxin destroys GI ganglionic cells—Hirschuspring-like effects!

T. Cruzi Medications (Story):

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifurtimox</td>
<td>Produces oxygen radicals</td>
<td>Nicole Kidman!</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Inhibits glycolysis</td>
<td>Penelope Cruz!</td>
</tr>
<tr>
<td>Suramin</td>
<td>Inhibits metabolism</td>
<td>Suri (his daughter!) Also the drug that sounds like “The last Samurai”</td>
</tr>
<tr>
<td>Benznidazole</td>
<td></td>
<td>His favorite car!</td>
</tr>
</tbody>
</table>
## HELMINTHOLOGY AND ANTIHELMinTHICS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trichinosis</strong></td>
<td>Trichina spiralis. Pig is the most common vector. Most common sites for muscle cysts: eye, biceps, jaw and diaphragm; Increased serum CPK. Thiabendazole (ETS inhibitor) and Mebendazole (inhibits microtubules and glucose uptake inhibitor).</td>
</tr>
<tr>
<td><strong>Ascariasis</strong></td>
<td>Largest human nematode. From GI to blood, to lung, and back to GI (with coughing); Eosinophilic pneumonitis. Mebendazole and Pyrantel (causes spastic paralysis of worm’s muscles by nicotinic excitatory agonistic action).</td>
</tr>
<tr>
<td><strong>Schistosomiasis</strong>&lt;br&gt;<strong>Blood Flukes</strong>&lt;br&gt;S. mansoni and haematobium. Swimming in snail infested ponds. Skin penetration, portal vein invasion, and urinary bladder. Chronic Lymphadenopathy, fever, hepatosplenomegaly, diarrhea, portal hypertension. Mistaken (and co-exists) with typhoid fever. Haematobium predisposes to squamous bladder carcinoma. Praziquantel (Paralyses the worms) Pyrantel and Praziquantel Paralyze!</td>
<td></td>
</tr>
<tr>
<td><strong>Echinococciosis</strong></td>
<td>Dogs; Liver, brain and lung cysts (hydatid cysts); Only one cyst. Definitive treatment: Surgical removal of cysts.</td>
</tr>
<tr>
<td><strong>Diphyllobothriasis</strong>&lt;br&gt;and <strong>Taeniasis</strong></td>
<td>Fish Tapeworm (Diphyllobothrium latum); Pork (Taenia solium); Beef (T. saginata); D. latum associated with B12 deficiency. Praziquantel.</td>
</tr>
<tr>
<td><strong>Enterobiasis</strong></td>
<td>Pinworms (Enterobius vermicularis). Leading cause of children’s anal itching; Praziquantel.</td>
</tr>
<tr>
<td><strong>Toxocariasis</strong>&lt;br&gt;<strong>Visceral and ocular larva migrans</strong></td>
<td>Puppy’s feces (Toxocara canis); Eosinophilia. Dead ends in humans. No treatment. Only glucocorticoids.</td>
</tr>
<tr>
<td><strong>Necator / Ancylostoma</strong></td>
<td>Hookworm; skin penetration! Microcytic Anemia.</td>
</tr>
<tr>
<td><strong>Wuchereria</strong>&lt;br&gt;<strong>Filariasis</strong></td>
<td>Threadworm; Lymphangitis; Eosinophilia; Elephantiasis. Ivermectin (binds to and activates glutamate-gated channels), and albendazole.</td>
</tr>
<tr>
<td><strong>Trichuris</strong></td>
<td>Whipworm. Bloody diarrhea; anemia; mebendazole.</td>
</tr>
</tbody>
</table>
**Must-Know Helminthic Diseases**

**Helminthology Check List**

<table>
<thead>
<tr>
<th>Worm</th>
<th>AKA</th>
<th>Mnemonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobius</td>
<td>Pinworm</td>
<td>Ate Pineapple!</td>
</tr>
<tr>
<td>Ascaris</td>
<td>Roundworm</td>
<td>Round Asscaris!</td>
</tr>
<tr>
<td>Trichuris</td>
<td>Whipworm</td>
<td>Whip Trick!</td>
</tr>
<tr>
<td>Necator and Ancylostoma</td>
<td>Hookworm</td>
<td>Hooker’s Neck! Naked Anus!</td>
</tr>
<tr>
<td>Strongyloides</td>
<td>Threadworm</td>
<td>Strong Thread!</td>
</tr>
<tr>
<td>Wuchereria</td>
<td>Filaria</td>
<td>Wicked Filaria!</td>
</tr>
</tbody>
</table>

**WARNING:** Toxic language!
The following mnemonic is now under investigation for explicit linguistic vulgarity! Please apply with caution.

18. Northwestern Medical Review
Answers:
- **EAT** = Enterobius, Ascaris and Trichuris
- Acquired by skin penetration: Schistosoma, Strongyloides and Hookworms
- Only Infect Humans: Strongyloides (Threadworms) and Pin Worms (Enrobius)
- Emigrate to lungs: Necator americanus, Ascaris, and Strongyloides
- NASA = American story! Necator americanus!
- Astronaut = Ascaris!
- Astronauts are strong! = Strongyloides!
- The all go to space (air/lung?)
- Crawl out of anal sphincter: Pin Worms (Enrobius)
- Squamous Bladder cancer: *S. haematobium*

What is the name of the disease in the following picture and what has caused it?

While evaluating the intestinal contents and mucosa of an immigrant farmer from a Caribbean Island we saw the following helminthes parasite. What is this?

What is Guinea worm disease and how is it treated?

What is the second most common infectious cause of blindness after trachoma?

What is the treatment for Onchocerciasis?

What is the most common parasitic cause of vitamin B12 deficiency?

Hint: The picture!
Starting with Desert Storm in 1991 and then the US wars in Afghanistan and Iraq last decade, a very high number of soldiers have contracted a disease that has become famous, mainly among the military personnel, as the Baghdad Boil. Which of the following options is the correct description for this disease?

A. Echinococcosis  
B. Diphyllobothriasis  
C. Onchocerciasis  
D. Stronglyloides  
E. Leishmaniasis

Starting with Desert Storm in 1991 and then the US wars in Afghanistan and Iraq last decade, a very high number of soldiers have contracted a disease that has become famous, mainly among the military personnel, as the Baghdad Boil. Which of the following options is the correct description for this disease?

F. Echinococcosis  
G. Diphyllobothriasis  
H. Onchocerciasis  
I. Stronglyloides  
J. Leishmaniasis

Matching question: Match the numbered statements (items) with the lettered options (helminthes) that are shown below:

1. Undercooked pork  
2. Raw fish consumption  
3. Plugs lymphatics  
4. Blindness  
5. Bladder cancer  
6. Cysts acquired from dogs  
7. Scotch-tape test  
8. They live their entire life cycle in our body

A. Filariasis  
B. Schistosoma hematobium  
C. Cysticercosis (pork tapeworm) and Trichinosis  
D. Stronglyloides  
E. Diphyllobothriasis  
F. Echinococcosis  
G. Pinworm  
H. Onchocerciasis

Answers

- The second most common cause of blindness is due to River blindness (Onchocerciasis). A nematode transmitted by black fly. The fly lives on the bank of rivers in Africa. Microfilaria may migrate to eye after inoculation and causes glaucoma and sclerosing keratitis.
- Treatment for Onchocerciasis: Ivermectin and Suramin
- B12 deficiency: Diphyllobothriasis (Fish tapeworm)
- Elephantiasis due to Wuchereria bancrofti, that is a human roundworm and it's the major cause of lymphatic filariasis. Spreads by mosquitoes. Other manifestation is Eosinophilia
- Guinea worm disease is also known as Dracunculiasis. The worm is acquired from contaminated water (with water fleas that have larvae of the guinea worm), encysts under the skin, then erupts after maturity; the only cure is to wrap the worm day-by-day, around a stick!
- Prophylactic Measure: Filtering water!
- This is Whip worm (Trichuris). The thin part often enters the mucosa and the thick part stays in the lumen of intestines. More often affects dogs and farm animals
- The correct answer is option “D” [IgE]
- Regarding Dessert Storm related Case: Leishmania [option E] is correct. It is transmitted by sand flies and affects approximately 350 million persons, primarily in the Middle East and Asia. During 2003, in excess of 650 soldiers contracted cutaneous leishmaniasis, which is the main manifestation of the disease. The soldiers coined the term Baghdad Boil for the disease. The skin sores of Leishmania are not painful or contagious, but if left untreated they can last up to two years and produce permanent skin scars. Note that Leishmaniasis occurs in two forms: the cutaneous form described above, and the visceral form (kala-azar), which is the most serious manifestation of the disease, affecting various internal organs.