49 – Lots of Protozoa

Speaker: Edward Mitre, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Lots of Protozoa

Edward Mitre, MD
Bethesda, MD

7/25/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Protozoa

Protozoa - Extraintestinal

Apicomplexa
- Plasmodium
- Babesia
- (Toxoplasma)

Flagellates
- Leishmania
- Trypanosomes
- (Trichomonas)

Amoebae
- Naegleria
- Acanthamoeba
- Balamuthia

Protozoa - Intestinal

Apicomplexa
- Cryptosporidium
- Cyclospora
- Cystoisospora

Flagellates
- Giardia
- Dientamoeba

Amoebae
- Entamoeba

Ciliates
- Balantidium

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

Protozoa

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Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

Question 1: A 54 yo woman presents with fever, chills, and oliguria one week after travel to Malaysia.

Vitals: **39.0** ° C, HR 96/min, RR 24/min, **BP 86/50**

Labs: Hct 31%, platelets14,000/μl, Cr of 3.2 mg/dL.

Peripheral blood smear has intraerythrocytic forms that are morphologically consistent with *Plasmodium malariae*.

The most likely infectious agent causing the patient's illness is:

A. Plasmodium malariae
B. Plasmodium knowlesi
C. Plasmodium vivax
D. Plasmodium falciparum
E. Babesia microti

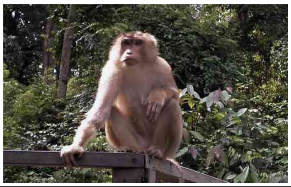
P. knowlesi

diagnosed in over 120 people in Malaysian Borneo

Lancet 2004;363:1017-24.

morphologically similar to *P. malariae*

usually a parasite of long-tailed macaques



increasingly recognized in Myanmar, Phillipines, Indonesia, and Thailand.

causes high parasitemia

highly morbid and can be lethal

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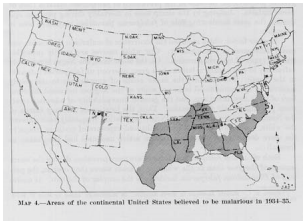
MALARIA

one of the most important pathogens in the history of the world

CDC arose from national Malaria Control programs



Map 4.—Areas of the continental United States believed to be malarious in 1934-35.

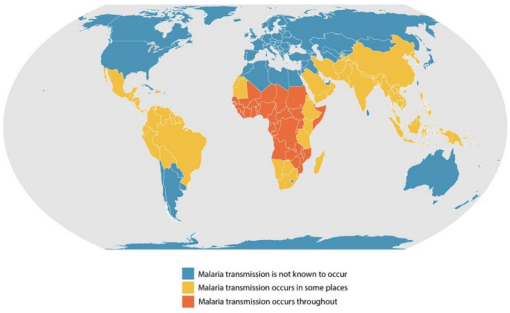
National Malaria Elimination Program: 1947- 1951
DDT spraying ~ 5 million homes and drainage of wetlands

→ Atlanta was chosen as the location for the Office of Malaria Control in War Areas (the predecessor agency of the CDC) in part because of its location in a malaria-endemic region
→ a main goal was to limit malaria at military training bases in the southern U.S.

CDC Name Changes (fyi)

1942-46:	Office of Malaria Control in War Areas (really the predecessor agency of the CDC)
1946-70:	Communicable Disease Center
1970-80:	Center for Disease Control
1980-1992:	Centers for Disease Control
1992-present:	Centers for Disease Control and Prevention

MALARIA EPIDEMIOLOGY



This map shows an approximation of the parts of the world where malaria transmission occurs.

https://www.cdc.gov/malaria/about/distribution.html

In non-immune patients, falciparum malaria is a medical emergency!!

→one of the most common causes of fever in a returned traveler

→ infected individuals can rapidly progress from appearing well to being critically ill

Family Feud: The Three Most Common Causes of Fever in a Returned Traveler.

1.
2.
3.

Family Feud: The Three Most Common Causes of Fever in a Returned Traveler.

1. **Malaria**
2. **Malaria**
3. **Malaria**

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---Some helpful heuristics---

If patient has	make sure patient doesn't have
Fever and freshwater contact---------->	
Fever and unpasteurized milk---------->	
Fever and undercooked meat---------->	
Fever and raw vegetables---------->	
Fever and untreated water---------->	
Fever and wild dog bite---------->	
Fever and abdominal pain---------->	
Fever and headache---------->	
Fever and diarrhea---------->	
Fever and cough---------->	
Fever and dysuria---------->	

---Some helpful heuristics---

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Fever and unpasteurized milk---------->	Malaria
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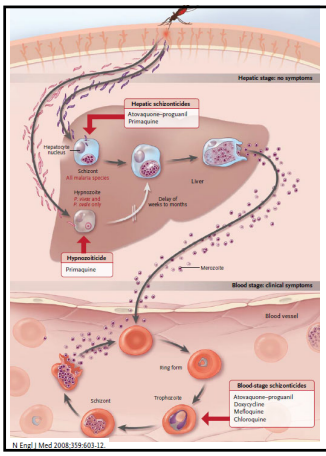
Fever and raw vegetables---------->	Malaria
Fever and untreated water---------->	Malaria
Fever and wild dog bite---------->	Malaria
Fever and abdominal pain---------->	Malaria
Fever and headache---------->	Malaria
Fever and diarrhea---------->	Malaria
Fever and cough---------->	Malaria
Fever and dysuria---------->	Malaria



N Engl J Med 2008;359:603-12.

Sporozoites
- **Infective stage**
- Come from mosquito

Liver schizont
- **Asymptomatic replicative stage**
- Become 10,000 to 30,000 merozoites

Hypnozoite
- Dormant liver stage in **vivax and ovale**
- Release merozoites weeks to months after primary infection

Merozoites
- Infect RBCs and develop into ring-stage trophozoites
- Mature into schizonts, which release merozoites which infect more RBCs

Gametocytes
- Infective stage for mosquitoes

characteristics of human malaria species

	P. falciparum	P. knowlesi	P. vivax	P. ovale	P. malariae
incubation	8 - 25 d	prob 8-25 d	~ 2 wks	~ 2 wks	~ 3-4 wks
hypnozoite	no	no	yes	yes	no
RBC age	any	any	young	young	old
parasitemia	high	high	< 2%	< 2%	< 1%
morbidity	high	high	high	moderate	low
mortality	high	moderate	low	low	low

Possible evolutionary defenses against malaria

Duffy antigen negative (*P. vivax* uses Duffy Ag to enter RBCs)

Sickle cell trait (increases survival during *P. falciparum* infection, perhaps by selective sickling of infected RBCs)

Glucose-6-phosphate dehydrogenase deficiency

(malaria parasites grow poorly in G6PD deficient RBCs, perhaps b/c this results in an overall increase in reactive oxygen species in RBCs)

Uncomplicated (mild) malaria

Symptoms: fevers, chills, headache, fatigue
***NOTE: abdominal pain presenting symptom in 20%**

→ periodicity of fevers not common when patients seen acutely

Labs: Thrombocytopenia in 50%
mild anemia in 30%
typically no leukocytosis
may see evidence of hemolysis with mild increase T bili and LDH

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Complicated (severe) malaria

- Cerebral malaria (altered mental status, seizures)
- Respiratory distress/pulmonary edema
- Severe anemia (hct <15% in children, <20% in adults)

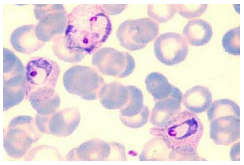
Often seen in children of endemic countries. Adults more often get multiorgan failure.

- Renal failure
- Hypoglycemia
- Shock (SBP < 80 mm Hg or capillary refill > 3 seconds)
- Acidosis (often lactic acidosis)
- Jaundice (total bilirubin > 3 mg/dL)
- Bleeding disorder (spontaneous bleeding or evidence of DIC)

These complications primarily occur with *Plasmodium falciparum,* usually when parasitemia >2%.

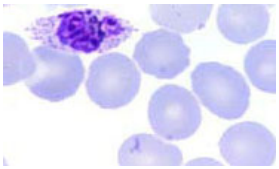
NOTE: in the absence of end organ damage, parasitemia >10% is often used as the cut-off to treat for severe malaria

P. vivax or ovale



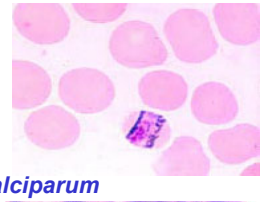
Both have
- intracellular Schüffner's dots
- enlarged infected cells

P. ovale



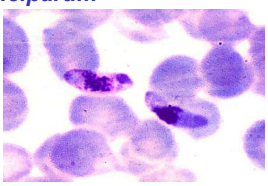
P. ovale
-elongated or oval
-6-12 merozoites (vs 12-24 for vivax)

P. malariae



-band form
(also seen in *P. knowlesi*)

P. falciparum

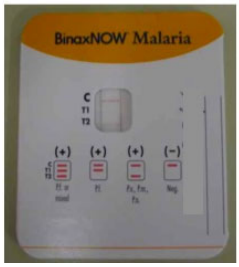


Banana shaped gametocyte

Malaria: Diagnosis

Rapid diagnostic (antigen capture) tests

→ sensitivity 95% for P. falciparum (about 85% for other species)



Binax Now® ICT assay for the detection of *Plasmodium falciparum* malaria according to the level of parasitemia

Parasitemia (no. of parasites/μL of whole blood)	Microscopy (no. positive)	NOW ICT (no. positive)	Sensitivity (%)
1–100	4	3	75.0
101–1,000	26	25	96.2
1,001–10,000	37	36	97.3
>10,000	34	33	97.1

Am. J. Trop. Med. Hyg., 69(6), 2003, pp. 589–592

for P. falciparum (T1) → tests for histidine-rich protein 2
for all species (T2) → tests for aldolase

Most false-negative antigen tests are due to low parasite burden. So, retest suspected patients that initially test negative.

Note: there are some false negative cases that have occurred due to mutations in HRP2 protein.

Question 2:

A 33-year-old woman is traveling to Uganda to do field studies in anthropology. She is two months pregnant. Which of the following do you prescribe for malaria prophylaxis?

A. Doxycycline
B. Chloroquine
C. Mefloquine
D. Atovaquone/progruanil
E. No prophylaxis

Malaria Chemoprophylaxis (note: no vax for travelers)

CENTRAL AMERICA and MIDDLE EAST

	Pre-Exposure	During	Post-Travel
Chloroquine 500mg tabs	1 tab/wk x 2 wks	1 tab/wk	4 weeks
EVERYWHERE			
Atovaquone/proguanil 250/100mg	1 tab daily x 2 d	1 daily	7 days
Doxycycline 100mg tabs	none	1 daily	4 weeks
Tafenoquine* 100mg tabs	2 tab daily x 3 d	2 tab/wk	2 tab after 1 wk
Mefloquine (not SE Asia)** 250mg tabs	1tab/wk x 2-3 wks	1 tab/wk	4 weeks

* *Tafenoquine can precipitate severe hemolytic anemia in individuals that are G6PD deficient*

** *FDA black box warning in 2013 that mefloquine can cause neurologic symptoms, hallucinations, and feelings of anxiety, mistrust, and depression. Can also cause QT prolongation. Thus, many U.S. practitioners now reserve mefloquine for pregnant travelers to areas with chloroquine resistance*

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Treatment of *P. falciparum*

Uncomplicated (no organ dysfunction, low parasitemia, able to take po)

if chloroquine sensitive area → chloroquine

if chloroquine resistant area

→ artemether/lumefantrine (Coartem) x 3 days
→ atovaquone/proguanil (Malarone) x 3 days
→ 2nd line: quinine x 3 days + doxycycline x 7 days

Severe

→ IV artesunate **FDA approved since May 2020**
(CDC malaria hotline: 770-488-7788 or -7100)

Note:

- Delayed-onset anemia common after Rx with artesunate
- Artemisin resistance has been reported in both SE Asia and parts of Africa
- IV quinidine has not been available in the U.S. since 2019

Treatment of *P. vivax*

chloroquine x 3 days and then…

- primaquine –weight based dosing and duration as determined by G6PD activity
  (usually 0.5 mg/kg primaquine base x 14 days if normal G6PD activity, if G6PD activity < 30% then can treat with 0.75mg/kg weekly for 8 weeks)

or

- tafenoquine (two 150 mg tabs)

→ Need to check G6PD status before administering primaquine OR tafenoquine as both can cause severe hemolysis in patients with G6PD deficiency

→ Primaquine requires cytochrome P-450 2D6 to be effective. Therefore, clinical failure to cure *P. vivax* can be due to low host levels of CYP450-2D6.
N Engl J Med 2013; 369:1381-1382

* Suggestions for all ID practitioners *

1) Make sure the facility where one works has the means to rapidly test for malaria

2) Ensure that hospital pharmacy has access to appropriate medications for treatment of malaria

Babesia

Transmission

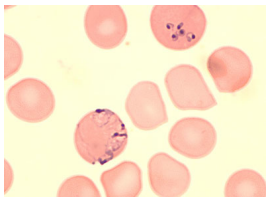
- Ixodes ticks in Northeast and upper midwest
  →co-infection with Lyme and Anaplasma
- Transfusion (approx. 1/20k in NE if un unscreened…Ab screening tests approved by FDA in 2018)

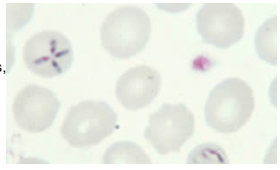
Symptoms: fever, headache, chills, myalgias
less common: nausea, dry cough, neck stiffness, vomiting, diarrhea, arthralgias
→ severe disease: in HIV, asplenia

Labs: anemia, thrombocytopenia, mild increase LFTs, normal/low/high WBC

Diagnosis: small ring forms in RBCs, PCR, Ab
merozoites can make tetrad ("Maltese cross")

Treatment: azithromycin + atovaquone
(clindamycin + quinine is alternative)
→ Exchange transfusion for severe disease





CDC DpDx

Protozoa

Protozoa - Extraintestinal

Apicomplexa
Plasmodium
Babesia
(Toxoplasma)

Flagellates
Leishmania
Trypanosomes
(Trichomonas)

Amoebae
Naegleria
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Ciliates
Balantidium

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

Leishmaniasis

→obligate intracellular protozoan infection
→transmitted by sand flies (noiseless, active in evenings)

Lutzomyia
New world leishmaniasis

Phlebotomus
Old world leishmaniasis

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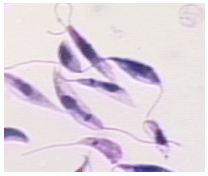
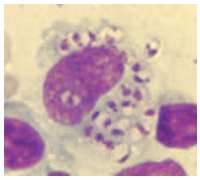
Leishmania life cycle – Two stages

Promastigote	Amastigote
extracellular, in sand fly	Intracellular (macrophages)
2μm wide x 20μm long	Round or oval
+ flagella	Wright-Giemsa:
large central nucleus	dark-purple nucleus
band shaped kinetoplast	small rod shaped kinetoplast





CDC DpDx

Question 3: A 42 yo man from Bolivia presents with nasal stuffiness and is found to have nasal septal perforation. Biopsy demonstrates intracellular amastigotes consistent with Leishmania.

Which is the most likely species?

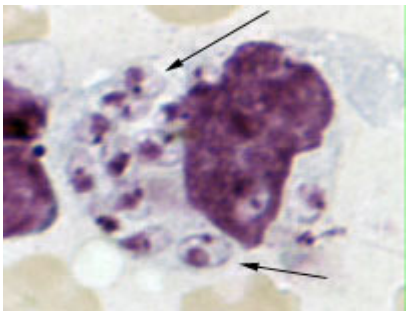
A. L. mexicana
B. L. braziliensis
C. L. peruviana
D. L. infantum chagasi
E. L. major

Leishmania taxonomy and disease simplified

	Cutaneous	Mucosal	Visceral
NEW WORLD			
L. mexicana complex	X		
L. braziliensis	X	X	
L. infantum chagasi			X
OLD WORLD			
L. tropica	X		
L. major	X		
L. donovani			X
L. infantum chagasi			X

*note: *L. braziliensis* is in the Viannia subgenus. *L. V. guyanensis* and *L. V. panamensis* also cause mucosal disease. *L. peruviana* DOES NOT

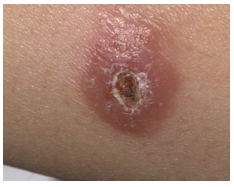
Here are some very clear amastigotes
→ intracellular organisms with nucleus and kinetoplast



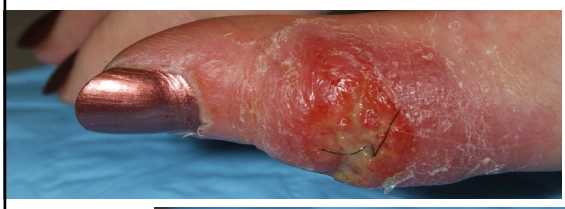
http://www.dpd.cdc.gov/dpdx/HTML/Leishmaniasis.htm

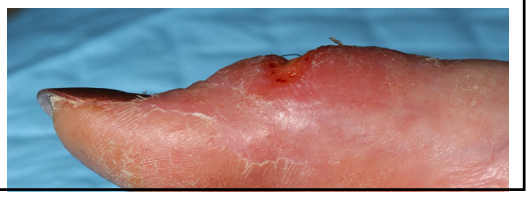
Cutaneous Leishmaniasis – Clinical Presentation

- **papule → nodule →ulcerative lesion → atrophic scar**
  - **ulcerative lesion may have:**
    - **induration,**
    - **scaliness**
    - **central depression**
    - **raised border**



- **takes weeks to months to develop**
- **usually painless, unless superinfected**
- **most lesions will eventually resolve on their own**





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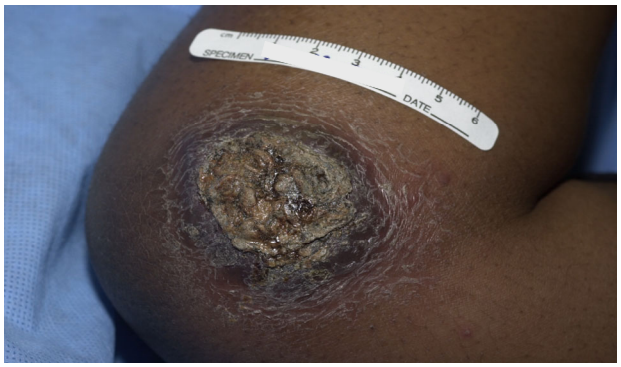
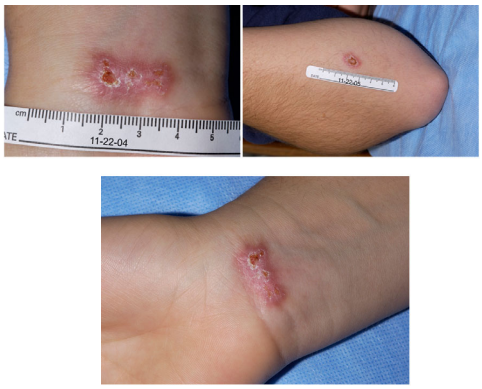
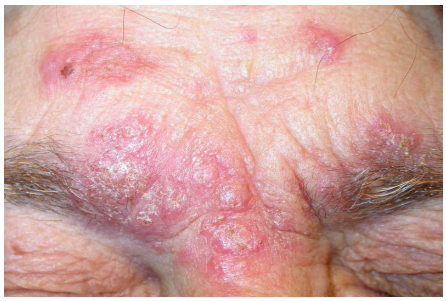






Cutaneous Leishmaniasis – Diagnosis

Definitive diagnosis is very helpful because

1. **Allows you to rule out other possibilities**
2. **May help in deciding whether and how to treat**

Diagnostic Tools (edge of ulcer skin: scraping, aspirate, punch)

Touch prep with examination under oil looking for amastigotes

Culture on triple N media (may take weeks to grow)

(Nicolle's modification of Novy and MacNeal's medium – biphasic)

Histology

PCR

Cutaneous Leishmaniasis – Treatment Recommendations

→ **Treat systemically if *L. (V.) braziliensis, guyanensis, panamensis***

→ **If not, ok to observe if there are:**

few lesions, they are < 5 cm, not on face/fingers/toes/genitals, normal host, no subcutaneous nodules

Treatment Options

local: heat with radiotherapy (FDA approved), cryotherapy, intralesional therapy

systemic

oral: miltefosine for certain species, especially New World CL species
ketoconazole, fluconazole (off-label)

IV: liposomal amphotericin B (off-label)

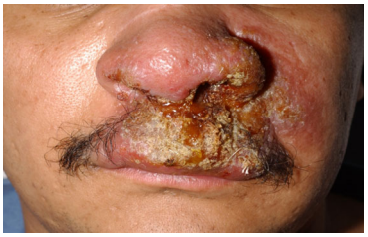
(June 2021:pentavalent antimony aka stibogluconate no longer avaialable from CDC on IND)

*****2016 IDSA GUIDELINES FOR TREATMENT OF LEISHMANIA*****
http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organism/Parasites/Leishmaniasis/

Mucosal leishmaniasis

Leishmania (Viannia) braziliensis, Guyanensis, panemensis

- dissemination to nasal mucosa
- slow, progressive, destructive
- can occur months or years after cutaneous ulcer



Treatment:
- oral miltefosine
  (FDA approved for *L. braziliensis*)
- IV lip. amphotericin (off-label)
- IV antimony (no longer available)

Miltefosine notes
side effects: nausea, vomiting, diarrhea, increased AST/ALT
contraindicated in pregnancy, use contraception for 5 months after treatment ($t_{1/2}$ = 30 d)

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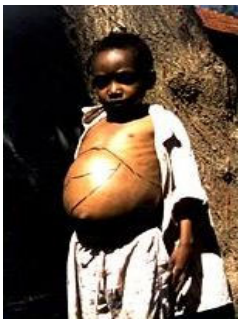
Visceral Leishmaniasis

L. donovani *(South Asia, East Africa)*

L. infantum chagasi *(Middle East, Central Asia, Mediterranean, Central and S. America)*



amastigotes in macrophages go to local LNs then hematogenously to liver, spleen, bone marrow

A peristent disease that can reactivate
TNF blockade, HIV CD4 < 200

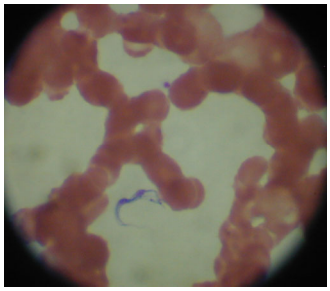
Weeks/months: fevers, chills, fatigue, hepatosplenomegaly

pancytopenia & hypergammaglobulinemia

Diagnosis: intracellular amastigotes in bone marrow or splenic aspirate
antibody to rK39 recombinant Ag (dipstick test)

Treatment: liposomal ampho B (FDA approved)
miltefosine (oral) FDA approved for *L. donovani*

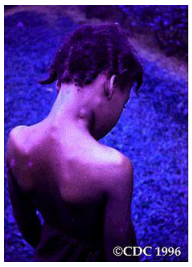
Question 4: A 41 yo woman presented to a local emergency department with a one day history of fever associated with swelling and redness in her groin four days after returning from safari in Tanzania. Peripheral blood smear is obtained.



What is the most likely diagnosis?

A. Leishmania donovani
B. Plasmodium vivax
C. Trypanosoma brucei
D. Wuchereria bancrofti
E. Leptospira interrogans

African Trypanosomiasis (sleeping sickness)



Vector = tse tse fly (Glossina sp)

Trypanosoma brucei gambiense (W. Africa)
- humans as reservoirs
- progression over many months

Trypanosoma brucei rhodesiense (E. Africa)
- cattle and game park animals as reservoirs
- progression over weeks

DISEASE
within 5 days: chancre at Tse Tse fly bite
regional lymphadenopathy

for weeks: fever, hepatosplenomegaly, lymphadenopathy, faint rash, headache

late: mental status changes, terminal somnolent state

African Trypanosomiasis – Lab findings

Non-specific lab findings
- anemia
- thrombocytopenia
- elevated IgM
- hypergammaglobulinemia

Diagnostic lab findings
- detection of parasite in lymph node, circulating blood, or CSF

-->do FNA of lymph node while massaging node, then push out the aspirate onto a slide and immediately inspect under 400x power. Trypanosomes can be seen moving for 15-20minutes, usually at edge of the coverslip

- a card agglutination test that detects T.b.gambiense sp. antibodies.
  -->V. sensitive (94-98%), but poor specificity
  --> can get false +s in pts with Schisto, filaria, toxo, malaria

African Trypanosomiasis - Life Cycle

Q. Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

African Trypanosomiasis - Life Cycle

Q. Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

A. because they keep changing their outer surface protein
- T. brucei contains as many as 1000 genes encoding different VSGs (VSG = variant surface glycoprotein)
- each trypanosome expresses one, and only one, VSG at a time
- individual parasites can spontaneously switch the VSG they express

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

African Trypanosomes – The Lady Gaga of the Microbial World

African Trypanosomiasis –Treatment

West African (T. gambiense)

If < 6 yo or < 20 kg: lumbar puncture

CSF < 5 WBC/ul → iv pentamidine

CSF > 5 WBC/ul → iv eflornithine + nifurtimox

If adult: confusion, ataxia, anxiety, abnl speech, motor weakness, abnl gait?

no suspicion of late disease → oral fexinidazole

if suspicion of CNS disease → obtain lumbar puncture

CSF < 100 cells/ul (non-severe 2nd stage) → oral fexinidazole

CSF > 100 cells/ul → iv eflornithine+ nifurtimox

East African (T. rhodesiense): Rx always guided by lumbar puncture

CSF < 5 WBC/ul → suramin

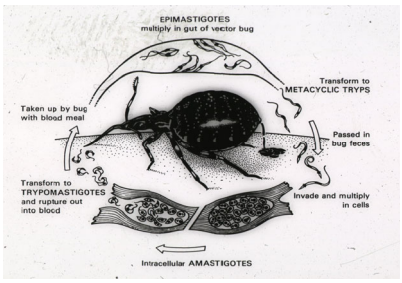
CSF > 5 WBC/ul → melarsoprol

Juy 16, 2021: Oral fexinidazole FDA approved for T. gambiense

Notes: 1) Melarsoprol associated with ~5% death rate due to reactive encephalopathy.
2) This is reduced by co-administration of corticosteroids.

Chagas disease

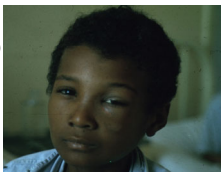
- transmitted by *Trypanosoma cruzi*
  (also blood transfusion and congenitally)
- vector: reduviid (triatomine) bugs
- reservoirs: opossums, rats, armadillos, raccoons, dogs, cats



Chagas – Clinical Disease

Acute (starts 1 week after infection, can persist for 8 weeks)

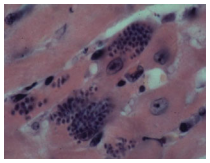
- fever
- local lymphadenopathy
- unilateral, painless periorbital edema



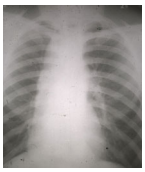
Indeterminate stage

- serology positive, no evidence of disease

Chronic

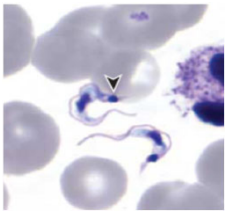


dilated cardiomyopathy, R>L
(CHF, syncope, arrythmia)



megaesophagus

Chagas Diagnosis & Rx



Acute disease

- identification of parasites in blood

Chronic disease

- *T. cruzi* specific IgG antibodies in serum
  → **two antibody tests using different antigens and different techniques recommended for dx**
  (research: xenodiagnosis, hemoculture, PCR)

NOTE: U.S. blood supply screened for 1st time donors

Treatment

Benznidazole for 30 – 60 d, alternative: Nifurtimox (both FDA approved)
Benznidazole AEs: peripheral neuropathy, granulocytopenia, rash
Nifurtimox AEs: abdominal pain/vomiting, tremors, peripheral neuropathy

Always offer: acute infection, congenital, < 18 yo, reactivation disease
Usually offer: 19-50 years old and no advanced cardiac disease
Individual decision: > 50 years old and no advanced cardiac disease

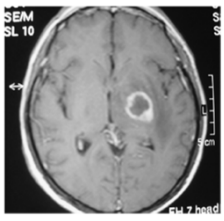
Chagas in immunosuppressed patients

T. cruzi and AIDS

Primarily reactivation neurologic disease

→ acute,diffuse, necrotic meningoencephalitis

→ focal CNS lesions (similar to Toxo)**



2008 Int J Infectious Diseases

T. cruzi and solid organ transplant

→ recipient of infected organ:
fevers, hepatosplenomegaly, myocarditis

→ disease often does not occur until months after transplant

ALSO…. reactivation myocarditis occurs in ~40% of patients that receive heart transplant because of Chagas cardiomyopathy

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

Protozoa

Protozoa - Extraintestinal

Apicomplexa
- Plasmodium
- Babesia
- (Toxoplasma)

Flagellates
- Leishmania
- Trypanosomes
- (Trichomonas)

Amoebae
- Naegleria
- Acanthamoeba
- Balamuthia

Protozoa - Intestinal

Apicomplexa
- Cryptosporidium
- Cyclospora
- Cystoisospora

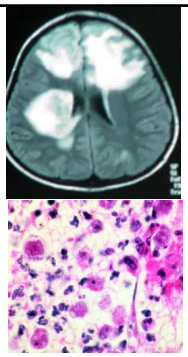
Flagellates
- Giardia
- Dientamoeba

Amoebae
- Entamoeba

Ciliates
- Balantidium

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

Free-living amoebae



Naegleria fowleri
- warm freshwater exposure
- enters through olfactory neuroepithelium
- fulminant meningoencephalitis
- immunocompetent children/young adults

Acanthamoeba
- found in soil and water
- enter through lower respiratory tract or broken skin
- subacute granulomatous encephalitis
- immunocompromised hosts
- chronic granulomatous keratitis (contact lens, LASIK)

Balamuthia mandrillaris
- likely enters through lower respiratory tract or broken skin
- transmission by solid organ transplantion has been reported
- subacute granulomatous encephalitis
- normal and immunocompromised hosts

Outcome → often fatal (amphotericin B, azoles, pentamidine, others tried)

Protozoa

Protozoa - Extraintestinal

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- Plasmodium
- Babesia
- (Toxoplasma)

Flagellates
- Leishmania
- Trypanosomes
- (Trichomonas)

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- Balamuthia

Protozoa - Intestinal

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- Giardia
- Dientamoeba

Amoebae
- Entamoeba

Ciliates
- Balantidium

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

When to suspect an intestinal protozoan infection:

Patient has: Protracted watery diarrhea (weeks to months)

AND/OR:
- **history of travel [domestic (esp. camping) or foreign]**
- **recreational water activities**
- **altered immunity (HIV infection)**
- **exposure to group care (daycare)**

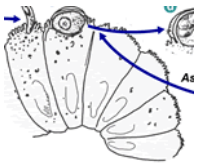
Note: discussion will focus on intestinal protozoa as they occur in patients seen in the U.S. These are leading causes of diarrhea, morbidity, and mortality worldwide, especially in young children.

Intestinal Apicomplexa parasites

Cryptosporidium
- *C. parvum:* cows
- *C. hominis:* humans

Cyclospora cayetanensis

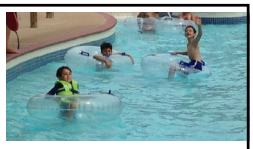
Cystoisospora belli



Cryptosporidium in enterocyte. CDC DpDx

- all have worldwide distribution
- all transmitted by water or food contaminated with oocysts
- organisms invade enterocytes
- all cause watery diarrhea that can be prolonged & severe in immunocompromised

Intestinal Apicomplexa: clinical clues



Cryptosporidium
- watery diarrhea of several weeks
- cattle workers and daycare outbreaks
- cysts are resistant to chlorine (water supply outbreaks)
  --> #1 cause of water park/swimming pool outbreaks

Cyclospora cayetanensis - self-limited immunocompetent BUT can last up to 10 weeks!

- abrupt onset with nausea, vomiting, and fever early
- anorexia, weight loss, fatigue late in course
- food associated outbreaks: raspberries, lettuce, herbs
- esp. Nepal, Peru, Guatemala

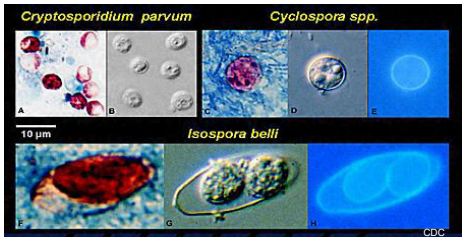
Cystoisospora belli
- no animal reservoirs known
- watery diarrhea
- may be associated with a peripheral eosinophlia!
  (the ONLY intestinal protozoa that does this)

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

Intestinal Coccidia characteristics

Pathogen	Size	Stain	Treatment
Cryptosporidium	4 μm	m acid-fast	(none) nitazoxanide or paromomycin
Cyclospora	10 μm	m acid-fast	TMP/SMX
Cystoisospora	20 μm	m acid-fast	TMP/SMX



Molecular tests

stool multiplex PCR detects cryptosporidium AND Cyclospora but NOT Cystoisospora

stool Ag tests commercially available for cryptosporidium

Morbidity and Mortality Weekly Report

Cryptosporidiosis Outbreaks — United States, 2009–2017

MMWR / June 28, 2019 / Vol. 68 / No. 25

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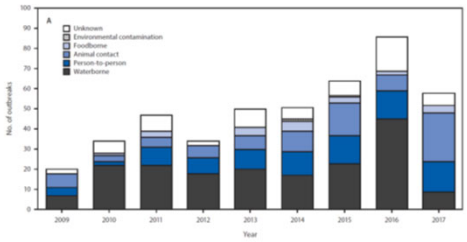


"The number of reported outbreaks has increased an average of approximately 13% per year."

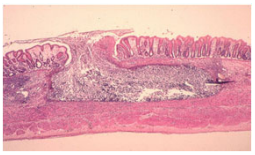
Question 5: A 28 year old woman returns after studying mosquito breeding habits in Honduras for one year. She reports intermittent abdominal pain and diarrhea for several months. Stool ova and parasite exam is positive for the presence of a ciliated single cell organism.

What is the most likely diagnosis?

A. Balantidium coli
B. Entamoeba histolytica
C. Giardia lamblia
D. Dientamoeba fragilis
E. Endolimax nana

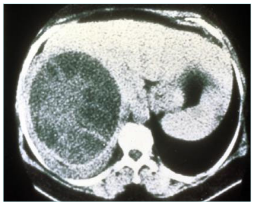
Entamoeba histolytica

- strictly human pathogen
- fecal/oral (contaminated food/water)
- cysts = infective stage
- trophozoites = active form, tissue-destructive



clinical presentations

- asymptomatic
- traveler's diarrhea
- colitis
  - sharp abdominal pain
  - bloody diarrhea
  - fever
  - flask-shaped ulcerations
  - →onset can occurs weeks to months after travel
- ameboma
- liver and brain abscesses, esp in young men, usually 2-5 months after travel



49 – Lots of Protozoa

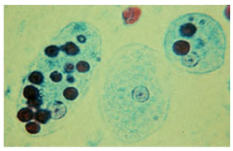
Speaker: Edward Mitre, MD

Entamoeba histolytica

Diagnosis

Stool PCR (multiplex or single)
- **close to 100% sensitivity and specificity**

Stool O/P
- only 50% sensitive for colitis and abscess
- poor specificity b/c unable to differentiate *E.histolytica* from non-pathogenic *E. dispar* and the diarrhea-only causing *E. moshkovskii*
  (note: ingested RBCs suggestive of Eh, but not 100%)



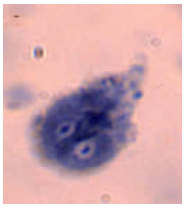
E. histolytica trophozoites with ingested RBCs.

Stool antigen testing > 85% sensitive for intestinal disease

Serology 95% sensitive for liver abscess, 85% sensitive for intestinal infection

Treatment
asymptomatic: luminal agents such as paromomycin
symptomatic: tissue agents such as metronidazole or tinidazole THEN luminal agent
liver abscess: medical therapy (tissue agent then luminal agent) usually sufficient!
drainage if no response to medical therapy or dx unclear or v large abscess

Giardia duodenalis → *described by Antony van Leeuwenhoek in 1681!*



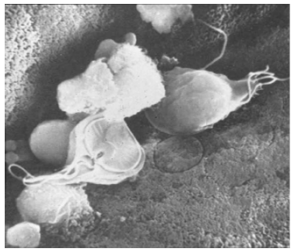
Flagellated protozoan
- fecal/oral via ingestion of cyst form in food/water
- cyst is chlorine resistant
- cysts from humans (beavers, muskrats)

Disease in U.S.
- most common parasitic infection in the U.S (20k cases reported/year, likely 2M)
  → U.S-acquired cases peak in the late summer/early fall
  → a leading cause of traveler's diarrhea

Symptoms
- intermittent watery diarrhea weeks to months
- foul smelling stools, flatulence, "sulfur burps"

Giardia

At risk populations
- international travelers
- swimming in lakes/streams, outdoor survival/camping
- infants in daycare
- child care workers
- immunoglobulin deficiencies (esp CVID)
- HIV when CD4 < 100



Diagnosis
- stool antigen test
- stool multiplex PCR

Treatment
tinidazole (FDA approved)
metronidazole (off-label), nitazoxanide (FDA-approved), and albendazole (off label)

Other intestinal protozoa

Non-pathogens

amoebae
- *Entamoeba dispar*
- *Entamoeba hartmanni*
- *Entamoeba coli*
- *Endolimax nana*
- *Iodamoeba bütschlii*

flagellates
- *Chilomastix mesnili*
- *Trichomonas hominis*

Treat if symptomatic: *Dientamoeba fragilis* (implicated in IBS)

Protozoa

Protozoa - Extraintestinal

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- Plasmodium
- Babesia
- (Toxoplasma)

Flagellates
- Leishmania
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Amoebae
- Entamoeba

Ciliates
- Balantidium

Not Protozoa

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

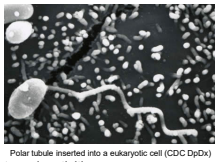
Microsporidia – obligate intracellular fungi!

→Produce extracellular, 1-2 micron, infective spores
→Spores have a coiled organelle called a polar tubule
→After ingestion, the spore germinates and the polar tubule is used to inject sporoplasm into a host cell

Spores of *E. hellem* bursting out of a cell (CDC DpDx)

Enterocytozoon bieneusi
- watery diarrhea
- biliary disease (cholangitis, acalculous cholecystitis)

Encephalitozoon intestinalis
- watery diarrhea
- biliary disease
- disseminated disease (liver, kidney, lung, sinuses)



Polar tubule inserted into a eukaryotic cell (CDC DpDx)

Encephalitozoon cuniculi, hellem
- can cause disseminated disease of multiple organs, plus eye

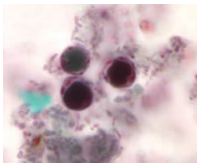
Many species (including *Vittaforma corneae*): punctate keratoconjunctivitis (contact lens use, after eye surgery, bathing in hot springs)

DIAGNOSIS: modified trichrome stain, Calcofluor white, IFA
TREATMENT: albendazole (not effective for *E. bieneusi*)

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

Blastocystis



Blastocystis cyst-like forms , trichrome (CDC DpDx)

What is it?

Nobody really knows!! Might be a protozoa.

Might also be a part of a new kingdom (Chromista!), with kelp and diatoms!

Forms are 5-40 microns wide. Anaerobic. Eukaryotic.
→ cystic, ameboid, granular, and vacuolar forms

Does it cause disease?
That's a good question!! Maybe.
Associated with watery diarrhea, abdominal discomfort, nausea, and flatulence.

Diagnosis: light microscopy of stool samples

Treatment?
metronidazole, tinidazole, TMP/SMX, or nitazoxanide (none FDA-approved)

Protozoan infections that can reactivate in the severely immunocompromised

- Toxoplasmosis
  - encephalitis with mass lesions
  - pneumonitis
  - retinitis
- Leishmania
  - reactivation of visceral and cutaneous reported
  - visceral with fever, hepatosplenomegaly, pancytopenia
- Chagas
  - encephalitis with mass lesions
  - hepatosplenomegaly and fevers
  - myocarditis in 40% that receive heart transplant b/c Chagas disease
- Malaria

Some other protozoa that can cause severe disease in immunocompromised

- Cryptosporidium
- Giardia
- Microsporidia
- Babesia
- Acanthamoeba

NOAA photo library

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