Introduction to Blood Parasites

It may be a bloody mess, but it is worth knowing

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Objectives for Learning

Understand the role of lab testing in blood parasite diagnostics

Recognize the major genera of blood parasites

Describe the clinical associations and syndromes of major blood parasites
Clinical Parasitology

- Organ systems:
  - Brain
  - Skin/Soft tissue
  - Lungs
  - Liver
  - GU
  - Blood

See separate video
Blood Parasite testing

• Blood smear overview

• Other methods discussed within organisms
Blood Smear Exam

• Collect peripheral or fingerstick blood
• Stain with Giemsa, Wright-Giemsa, or Wright
• Two smears:
  » Thick
    ▪ Increased sensitivity (more blood examined) & blood is lysed
    ▪ Detect parasites, may not allow full identification
  » Thin
    ▪ Morphology within in-tact blood cells is maintained
    ▪ Species determination achievable
    ▪ Parasite burden (parasitemia) can be determined
Blood Smear Exam

• Repeat every 6-8 hrs x3 if first test is negative & high clinical suspicion

Plasmodium falciparum thin smear

Plasmodium falciparum thick smear

https://www.cdc.gov/dpdx/
Major Blood Parasites

• Protozoa
  » Malaria (*Plasmodium* spp.)
  » *Babesia*
  » *Trypanosoma*

• Helminths – filarial nematodes
  » Lymphatic filariasis – *Wuchereria* & *Brugia* spp.
  » *Loa loa*
  » *Mansonella*

• Spirochetes*  
  *Not technically parasites*
Malaria – *Plasmodium* spp.

- Protozoan blood parasite > 150 species
  - 4 species are primary human parasites
    - *Plasmodium falciparum*
    - *Plasmodium vivax*
    - *Plasmodium ovale*
    - *Plasmodium malariae*

- Symptoms
  - Common: fever & chills (cycling)
    - Can be accompanied by headache, myalgias, arthralgias, weakness, vomiting, & diarrhea.
    - Less common: splenomegaly, anemia, thrombocytopenia, hypoglycemia, pulmonary or renal dysfunction, & neurologic changes

https://www.cdc.gov/parasites/malaria/index.html
**Plasmodium spp. Lifecycle**

- *Anopheles* mosquito vector
- Replicates in liver → blood
- Sexual replication → gametocytes
  - Transmissible form
- Erythrocytic cycle
  - Red blood cell replication/destruction

https://www.cdc.gov/dpdx/
Plasmodium falciparum

- Most dangerous → infects all types of red blood cells
  - Highest parasitemias
  - Severe symptoms include cerebral malaria (often fatal in children)

- Most commonly encountered in clinical care

- Most widespread

- Fevers cycle every 24-48 hours
  - Continuous at high parasitemia
Plasmodium falciparum

• Microscopy:
  » Small ring forms and banana-shaped gametocytes

https://www.cdc.gov/dpdx/
Plasmodium falciparum

Appliqué form

“Headphones”

Maurer’s clefts
**Plasmodium vivax**

- Prefers to infect macrocytic (immature) red blood cells
  - Low parasitemia = restricted host cell availability
    - Rare complication: splenomegaly or splenic rupture
- Second most common species in clinical care
  - Widespread
- Fevers every ~48 hours
- Liver phase hypnozoites can reactivate months after infection
Plasmodium vivax

Ring form trophozoite

Mature trophozoite w/Schüffner's dots
Plasmodium vivax

Gametocyte

Schizont

https://www.cdc.gov/dpdx/
**Plasmodium ovale**

- Prefers to infect macrocytic (immature) red blood cells
  - Low parasitemia = restricted host cell availability

- Third most common species in clinical care
  - Most geographically constrained

- Fevers every ~48 hours

- Liver phase hypnozoites can reactivate months after infection
Plasmodium ovale

Trophozoite

Trophozoite w/ fimbriation

Schizont

https://www.cdc.gov/dpdx/
Plasmodium ovale

Mature Trophozoite w/Schüffner's dots & fimbriation
Plasmodium malariae

- Prefers to infect senescent (older) red blood cells
  » Very low parasitemia = restricted host cell availability

- Fourth most common species in clinical care
  » Often asymptomatic
  » Constrained geographically

- Fevers every 72 hours (if any)
Plasmodium malariae

Trophozoite, gametocyte, & schizont

Band form trophozoite
Plasmodium malariae

Bird’s eye

Basket form
Regarding “other” *Plasmodium* sp.

Tread carefully with the hyperbole
Simian malaria

• Zoonotic malaria, rarely found in humans:
  » *Plasmodium knowlesi* - SE Asia/Malaysian peninsula
  » *Plasmodium cynomolgi* - Peninsular Malaysia
  » *Plasmodium schwetzi* - Tropical Africa
  » *Plasmodium coatneyi* - Peninsular Malaysia & Philippines
  » *Plasmodium inui* - Southeast Asia
  » *Plasmodium simiovale* - Sri Lanka and Malaysia
  » *Plasmodium simium* South America
    ▪ Probable *P. vivax* → jumped to monkeys after introduction.
  » *Plasmodium brasilianum* South America
    ▪ Probable *P. malariae* → jumped to monkeys after introduction.
**Plasmodium knowlesi**

- Simian malaria: narrow geographic distribution S.E. Asia
  - Malaysia, Indonesia

- Mimicry:
  - Clinically → *P. falciparum*
  - Morphology →
    - Early, *P. falciparum*
    - Late, *P. malariae* (but parasitemia too ↑)
  - NAAT → *P. vivax* if not carefully designed

https://www.cdc.gov/dpdx/
Plasmodium *knowlesi* – final note of caution

- Do not default to *P. knowlesi*
  - RARE $\Rightarrow$ consider common things being common

- Evaluate morphology $\Rightarrow$ Follow the flow
  - IF, something seems “odd”
  - THEN, consider other species like *P. knowlesi*

- CONFIRM appropriate geographic exposure

- Consider NAAT

https://www.cdc.gov/dpdx/
Malaria Treatment

• Depends on: severity, species, area acquired, previous anti-malarials used

• Resistance is a problem
  ▪ *P. falciparum & P. vivax*
    » See algorithm for detailed decision making: https://www.cdc.gov/malaria/resources/pdf/treatment_algorithm_101619.pdf
    » Acquired in area w/out chloroquine resistance → chloroquine
    » Acquired in area w/chloroquine resistance →
      ▪ (1) artemether-lumefantrine
      ▪ (2) atovoquone-proguanil
      ▪ (3) quinine + doxycycline
      ▪ (4) mefloquine

• Liver phase hypnozoites also require specific therapy
  ▪ *P. vivax & P. ovale* → tafenoquine or primaquine phosphate

https://www.cdc.gov/dpdx/
Other Malaria Tests

NAAT & Antigen
**Plasmodium** antigen from blood

- Rapid Diagnostic Test - Binax Now Malaria (only FDA cleared assay)
  - Results in < 30 min (good for hospitals unable to do blood smears)
    - But...less sensitive than blood smear examination

- Most sensitive for *P. falciparum*
  - Can detect three remaining human species
  - May cross-react with simian species

- 5000 parasites/ml = 0.125% parasitemia
NAAT for Malaria

• Not standard of care for Dx

• Excellent specificity and sensitivity (design dependent)

• Helpful for:
  » Possible mixed infections
  » Very low parasitemia specimens
    ▪ Few organisms to determine *Plasmodium* sp.
    ▪ *Babesia* vs *Plasmodium*
    ▪ *P. knowlesi* rule in/out

• Not truly quantitative, still requires parasitemia by smear

https://www.cdc.gov/dpdx/
Babesiosis

- Caused by apicomplexan parasites in the genus *Babesia*.  
  » Primary morphologic differential for malaria

- Transmitted by ticks in the genus *Ixodes*.

- Several species endemic to North America
  - *B. microti*, NE
  - *B. duncani*, West, PNW
  - *Babesia* MO-1, PNW, Missouri River Valley
Life Cycle of *Babesia microti*

Babesiosis

• Symptoms – often asymptomatic
  » When present, usually non-descript (fever, chills, sweating, myalgia, fatigue, hepatosplenomegaly); hemolytic anemia possible.

• Symptoms most severe in immunocompromised, elderly, asplenic patients.

• Diagnosis primarily by blood film examination
  » Species cannot be separated morphologically. NAAT or serologic testing needed for species-level ID (epidemiologic data can be helpful).
**Babesia - Morphology**

- ‘Maltese Cross’
- Extracellular forms
- Pleomorphic rings

[https://www.cdc.gov/dpdx/babesiosis/index.html](https://www.cdc.gov/dpdx/babesiosis/index.html)
Trypanosoma

• Protozoa (flagellate), two primary human pathogens

  » *T. cruzi* – causes Chagas disease

  » *T. brucei* – causes African sleeping sickness
Trypanosoma cruzi

• Vectored by triatomine bug (kissing bug)
  » Parasite in feces of bug, enters wound or mucus membrane

• Symptoms:
  » Acute: often asymptomatic, chagoma (node or lesion around bite site), Romaña sign is swelling around eye (@ bite)
    ▪ +/- fever, malaise
    ▪ Rarely cardiac or CNS involvement
Trypanosoma cruzi

• Symptoms:
  » **Chronic:**
    - Cardiac and/or GI involvement
  
  » ~70-80% remain chronically infected, asymptomatic for life (Indeterminate form)
  
  » 20-30% progress to disease over years to decades (Determinate form)
    - Megacolon
    - Cardiomyopathy
    - Megaesophagus
Trypanosoma cruzi

• Diagnosis:
  » Acute ➔ Microscopy (blood, CSF, biopsy)
    PCR
    Culture
  » Chronic ➔ Serology
    ▪ Recommend two different IgG serology tests to optimize accuracy

• Treatment: most effective for acute phase
  » Benznidazole (FDA cleared)
  » Nifurtimox (via CDC; investigational)

https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html
Trypanosoma brucei

- Vectored by Tse tse fly (Glossina) bite

- Humans are main reservoir
  » Occasionally cattle
Trypanosoma brucei

• Symptoms:
  » Early:
    ▪ Hard painful skin ulcer
    ▪ Fever
    ▪ Enlarged lymph nodes
  
  » Later:
    ▪ Symptom free (intermediate duration)
  
  » Late/end stage disease
    ▪ Somnolescence to coma
Trypanosoma brucei

- Two subspecies (cannot be distinguished morphologically):
  - *T. b. gambiense* (Gambling out west)
  - *T. b. rhodesiense* (Rhode Island is east)

<table>
<thead>
<tr>
<th>Subspecies</th>
<th>Parasitemia</th>
<th>Severity</th>
<th>CNS tropism</th>
<th>Time to CNS</th>
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</thead>
<tbody>
<tr>
<td>ssp. gambiense</td>
<td>↓</td>
<td>Less severe</td>
<td>Less tropic</td>
<td>Years</td>
</tr>
<tr>
<td>ssp. rhodesiense</td>
<td>↑</td>
<td>More severe</td>
<td>More tropic</td>
<td>&lt;9 months</td>
</tr>
</tbody>
</table>

Trypanosoma brucei

• Diagnosis:
  » Acute → Microscopy (blood, lymph aspirate, chancre fluid, bone marrow)
  » Chronic → Microscopy (CSF)

• Treatment: subspecies and source dependent
  » T. b. rhodesiense
    ▪ Hemolymphatic – Suramin
    ▪ CNS - Melarsoprol
  » T. b. gambiense
    ▪ Hemolymphatic – Pentamidine
    ▪ CNS - Eflornithine

https://www.cdc.gov/parasites/sleepingsickness/health_professionals/index.html#tx
Filariases

• Caused by various genera and species of filarial nematodes.

• Vector-borne

• Adults reside in various locations:
  » Lymphatic filariasis (lymph tissue)
  » Loiasis (skin, eye)
  » Mansonellosis (mesenteries, connective tissue, skin)

• Diagnosis primarily by detection of microfilariae in blood films
  » Serology for lymphatic filariasis
Lymphatic filariasis

• Caused by *Wuchereria bancrofti* (Circumtropical), *Brugia malayi* and *B. timori* (Southeast Asia)

• Vectors: mosquitos

• Clinical presentation: lymphatic filariasis (‘elephantiasis’)

Microfilaria of *W. bancrofti* in blood

https://www.cdc.gov/dpdx/index.html
Lymphatic filariasis

• Diagnosis:
  » Microfilariae in blood
  » Serology

• Treatment: diethylcarbamizine (DEC)
  » Contraindicated in patients with Onchocerca or Loa.
Loiiasis

• Caused by *Loa loa*, the African eye worm, endemic to west-central Africa

• Vectors: deer flies

• Clinical presentation:
  » ‘Calabar swellings’
  » ectopic migration to the eye

https://www.cdc.gov/dpdx/monthlycasestudies/2011/case301.html
Loiiasis

• Diagnosis:
  » Microfilaria in blood films
  » Adults removed from the eye

• Treatment: DEC
  » Albendazole to lessen worm burden prior to DEC administration

https://www.cdc.gov/dpdx/monthlycasestudies/2011/case301.html
Mansonellosis

• Three species:
  » *Mansonella perstans* (Africa, Latin America, Caribbean)
  » *Mansonella ozzardi* (Latin America, Caribbean)
  » *Mansonella streptocerca* (Africa)

• Vectors: biting midges (all 3), also black flies (*M. ozzardi*)

• Diagnosis: microfilariae in blood [often incidental]
  » *M. streptocerca* in skin snips

• Treatment: no standards; DEC + mebendazole; also ivermectin

*Mansonella perstans*, thin blood smear

https://www.cdc.gov/dpdx/index.html
Relapsing Fever  Borreliosis

- Not a parasite: caused by *Borrelia* spp. in the relapsing fever group
  » Vectored by soft ticks (*Ornithodorus*)

- Detected in blood smears
  (intentionally or accidental)

- Recurring febrile episodes ~3 days
  separated by afebrile period ~7 days
  » 75%: headache, myalgia, chills, nausea
  » 50%: arthralgia, vomiting
  » 25%: abdominal pain, dry cough, eye pain, diarrhea,
      photophobia, neck pain

[Link to CDC website]
https://www.cdc.gov/relapsing-fever/clinicians/index.html
Relapsing Fever  Borreliosis

• Diagnosis:
  » Blood smear
  » NAAT (most sensitive)
  » Serology (retrospective)

• Treatment:
  » Doxycycline
Approximate geographic ranges in the USA

Worldwide distribution for other species
Key Points

• Malaria – Anopheles mosquitos
  » *P. falciparum* – most dangerous, most widespread, chloroquine resistance
  » *P. vivax* – liver phase reactivation, chloroquine resistance
  » *P. ovale* – liver phase reactivation
  » *P. malariae* – mild or asymptomatic

• *Babesia* – tick-borne, asplenic patients @ high risk

• *Trypanosoma cruzi* – Chagas disease, Americas, chronic
  (e.g. cardiomyopathy, megacolon)

• *Trypanosoma brucei* – African sleeping sickness, blood microscopy,
  mostly fatal if untreated
Key Points

• Filariasis
  » *Wuchereria* – lymphatic filariasis and elephantiasis
  » *Loa loa* – African eye worm, Calabar swellings
  » *Mansonella* – often an incidental finding when blood films ordered for something else

• Tick-borne Relapsing Fever – soft ticks, widespread, cycling fevers
A nonprofit enterprise of the University of Utah and its Department of Pathology