TREATMENT OF TROPICAL DISEASES THAT MAKE IT TO THE UNITED STATES

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DISCLOSURE INFORMATION

- I have no financial relationship to disclose
- I will discuss the following FDA off-label and/or investigational use in my presentation:
  - Several of the treatments discussed are not approved by the FDA because of the low-incidence of these diseases within the United States

OBJECTIVES

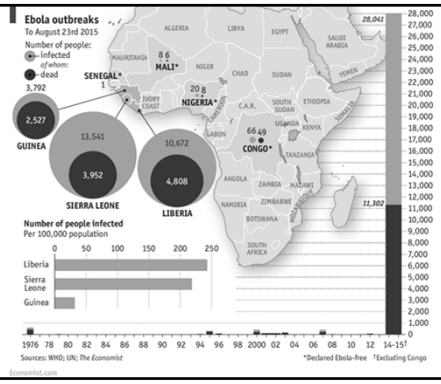
At the completion of this activity, the participant will be able to:

- Describe the symptoms of Ebola, Chagas, Malaria, Dengue, Lassa and Chikungunya
- Identify the current treatment of Ebola, Chagas, Malaria, Dengue, Lassa and Chikungunya
- Describe transmission of Ebola, Chagas, Malaria, Dengue, Lassa and Chikungunya
- Discuss current research on treatments and vaccines for the tropical diseases
- Compare and contrast the tropical diseases to each other

EBOLA VIRUS DISEASE (EVD)

2014 WEST AFRICA OUTBREAK

- According to WHO there have been 28,454 infections with > 11,207 deaths in the current outbreak in West Africa (as of 10/14/2015)
- Still some transmission in Guinea and Sierra Leone
- Liberia, Nigeria, Mali, Spain, United States and Senegal declared EVD free



2014 WEST AFRICA OUTBREAK

- Outbreak has been traced back to a 2 yo child in Guinea whose symptoms began on December 2, 2013 and died December 6, 2013.
- Unknown how the child got EVD
- Suspected to be contact with a fruit bat

EVD EPIDEMIOLOGY

- First identified in 1976 in 2 different countries
  - Sudan
  - Zaire (now the Democratic Republic of the Congo)
- 2 distinct species Ebola Virus in 1976
  - Ebola Sudan
  - Ebola Zaire

PATHOGENESIS

- Ebola enters through mucous membranes, skin breaks, or parenteral routes
- Ebola virus has been isolated in:
  - Nasal secretions
  - Saliva
  - Sweat
  - Semen
  - Genital secretions

INITIAL SYMPTOMS

- Fever
- Chills
- Malaise
- Myalgia

- Easy to confuse with other viral infections

SUBSEQUENT SYMPTOMS

- GI
- Respiratory
- Vascular
- Convulsions
- Metabolic disturbances
- Liver Failure
- Kidney Failure
- Skin

HEMORRHAGIC SYMPTOMS

- Present in less than 50% of cases
- When it occurs it is typically limited to GI
- Not enough blood loss to lead to death
- Exact mechanism is unknown
- Coagulation irregularities are seen
- Thrombocytopenia, loss of clotting factors, fibrin degradation

DIAGNOSIS

- Large differential diagnosis
- Labs will utilize:
  - RT-PCR
  - ELISA
  - Direct viral identification
- Can also look for IgM or IgG antibodies

TREATMENT

- Isolation of patient
- Symptomatic and supportive care
  - Fluids
  - Electrolytes
  - Antibiotics
  - Antipyretics
  - Dialysis
  - Respiratory support
  - Shock management

ZMAPP

- Made up of 3 “humanized” monoclonal antibodies
- Has shown response in a monkey model of Ebola Zaire (100% survival in 18 rhesus monkeys)
- Unknown at this time about humans
- Recombinantly manufactured
- 5 of 7 patients treated with ZMapp survived
- Ramping up production but still limited
- However production in mammalian cells being looked at

TKM - EBOLA

- Made up of small interfering RNAs that target proteins within the Ebola virus
- Phase I trial is currently on a "partial hold"
- This means the trial has been suspended but that patients with Ebola may be given access to it under the "Expanded Access Program"
- Phase II trial stopped enrolling new subjects June 19, 2015 because it "was unlikely to demonstrate an overall therapeutic benefit to patients".

BLOOD PRODUCTS

- Human convalescent plasma, whole blood, and other blood-derived therapies
- Theory is based on IgG antibodies against Ebola in the blood of survivors for 10+ years as well as anecdotal evidence
- Has been used within the US and in West Africa in current outbreaks
- Success rate is unknown at this point

EXPERIMENTAL THERAPIES

- Antibodies
- Antisense oligonucleotides
- Inflammatory modulators
- Coagulation modulators
- Antivirals
  - Favipiravir
  - Brincidofovir

VACCINES

- Chimpanzee adenovirus serotype 3 (cAd3-ZEBOV)
  - Uses a chimpanzee adenovirus with a gene for an EVD surface protein
  - A study in 16 animals showed 100% protection after a single dose
  - Human trials have started

VACCINES

- Recombinant Vesicular Stomatitis (VSV-EBOV)
  - Aims to induce EVD-specific immune responses
  - A study in 20 animals protected all of them from EVD
  - Trial in humans is underway

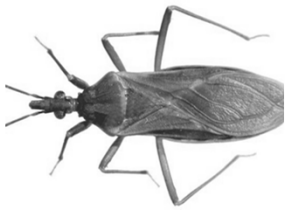
CHAGAS

- Also known as American trypanosomiasis
- Potentially life-threatening
- Caused by protozoan *Trypanosoma cruzi (T. cruzi)*
- Endemic throughout Central and South America
- Increasing incidence in the rest of the world
- 6-7 million people estimated to be infected worldwide
- CDC estimates 300,000 infected in the US
- Are cases of autochthonous transmission in the US

CHAGAS - TRANSMISSION

- *T. cruzi* is found in the feces of triatomine bugs (Kissing bugs)
- Triatomine bugs typically live in the house
- Tend to bite exposed skin at night
- Defecate as they are biting
- Feces is then rubbed into the bite, eyes, mouth
- Can be transmitted other ways as well

Triatomine bug occurrence by state



CHAGAS – ACUTE PHASE

- Some are asymptomatic
- Most cases have nonspecific symptoms
- Mild symptoms
  - Fever
  - Swelling at site of infection
  - Rashes
  - Wheezing
  - N/V

CHAGAS – CHRONIC PHASE

- Parasites can remain hidden in heart and digestive muscle
- ~75% of chronic cases are asymptomatic
- ~25% of chronic cases have cardiac and/or digestive abnormalities

- Cardiac
  - Arrhythmias
  - HF
  - Thromboembolic events
  - Valvular dysfunction
- Digestive
  - Megacolon
  - Esophagitis
  - Constipation
  - Dysphagia

CHAGAS - TREATMENT

- Benznidazole (available from CDC only – 404-639-3670)
  - useful for acute phase, indicated for chronic phase but less effective
  - Weight based and twice daily for up to 60 days
  - Take with food
  - Pregnancy – unknown, but not recommended in 1st trimester
  - Lactation - unknown, but suspected to be safe
  - ADRs (~40% of patients)
    - N/V
    - Anorexia
    - Insomnia
    - Peripheral neuropathy
    - Dermatitis
    - Disulfiram-like reaction

CHAGAS - TREATMENT

- Nifurtimox (available from CDC only – 404-639-3670)
  - Weight based 2-4 times a day for up to 90 days
  - Take after meals
  - Pregnancy - unknown
  - Lactation – unknown, but suspected to be safe
  - ADRs (tend to be worse than benznidazole)
    - Anorexia/weight loss
    - Polyneuropathy
    - N/V
    - Headache
    - Dizziness/vertigo

CHAGAS - RESEARCH

- Mostly vector control
  - Large reservoirs of animal hosts in Central and South America
- Several potential vaccine candidates
- Little research in new drugs

MALARIA

- Caused 584,000 deaths in 2013. Mostly African children
- 198 million cases of malaria in 2013
- Approximately 1500-2000 cases in US each year
- Dependent on:
  - Mosquito lifespan
  - Ambient temperature
  - Population density
  - Mosquito's biting habits
  - Host immune response
  - Drug activity

MALARIA - TRANSMISSION

- Transmitted by the bite of the *Anopheles* mosquito
- Four protozoal parasite species that cause malaria
  - *Plasmodium falciparum*
  - *Plasmodium vivax*
  - *Plasmodium malariae*
  - *Plasmodium ovale*
- Two distinct patterns of transmission
  - Stable malaria
  - Unstable malaria

MALARIA – SYMPTOMS

- Some are asymptomatic
- Most experience
  - Fever
  - Headache
  - Chills
  - Vomiting
- Severe
  - Anemia
  - Metabolic acidosis
  - Respiratory depression
  - Cerebral edema
  - Hypoglycemia

MALARIAL MANAGEMENT

- All patients will need antimalarial treatment
- Many patients will need antipyretics and analgesics
  - APAP or Ibuprofen
  - Avoid ASA in children
- Assess ABCs

MALARIAL MANAGEMENT

- Treat hypoglycemia
- Watch for bacterial co-infection
- Treat dehydration
- Oxygen/mechanical ventilation
- Inotropic therapy

ARTEMISININ-BASED COMBINATION THERAPIES (ACTS)

- Treatment of choice for uncomplicated falciparum malaria
- Combo of artemisinin derivative and another antimalarial
- Reduces spread of resistance
- Same principle as treatment of HIV/AIDs and TB
- Developing resistance to artemisinin drugs in southeast Asia and also be aware of resistance to "partner drugs"
- Non-artemisinin based combo therapies are not recommended

CURRENTLY RECOMMENDED ACTS

- Artemether + lumefantrine (Co-artem™, Riamet ™)
- Artesunate + mefloquine
- Artesunate + sufadoxine-pyrimethamine (not available in US)
- Artesunate + amodiaquine (not available in US)
- Many in development

PRIMAQUINE

- Indication
  - Treatment of malaria
  - Treatment of liver-stage malaria to give a radical cure
- Dose
  - Adults:
    - Malaria – 0.25mg/kg daily for 14 days
    - Liver stage – 0.25-0.5mg/kg daily for 14 days
  - Peds:
    - > 4 years old - 0.25-0.5mg/kg daily for 14 days

MALARIA - VACCINES

- Development is difficult
- Currently no commercial vaccine available
- RTS,S/AS01 currently in Phase 3 trials and showed a 51% efficacy in reducing falciparum malaria in infants 5-17 months with full data expected to be available soon
- Currently there are at least 20 other malaria vaccines that are in early testing; they are at least 5-10 years behind RTS,S

DENGUE FEVER

- Global disease of mostly tropical and sub-tropical areas
- Usually feel better within a week
- WHO estimates 50-100 million infections per year
- WHO estimates 22,000 deaths per year
- Several thousand cases imported into US each year
- At least 6 cases acquired in Florida in 2014

DENGUE - TRANSMISSION

- Caused by Dengue virus
  - 4 different serotypes
- Transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes
- Thought to have emerged in Africa/ Southeast Asia initially
- Now endemic in > 100 countries

DENGUE – COMMON SYMPTOMS

- High fever
- Severe headache
- Severe eye pain,
- Joint pain
- Muscle and/or bone pain
- Rash

DENGUE – SEVERE SYMPTOMS

- Severe dengue (SD) is a potentially deadly complication due to:
  - plasma leaking
  - fluid accumulation
  - respiratory distress
  - severe bleeding
  - organ impairment
- SD warning signs occur 3–7 days after the first symptoms in conjunction with a decrease in temperature (below 38°C/ 100°F) and include:
  - severe abdominal pain
  - persistent vomiting
  - rapid breathing
  - bleeding gums
  - fatigue
  - restlessness
  - blood in vomit

DENGUE - TREATMENT

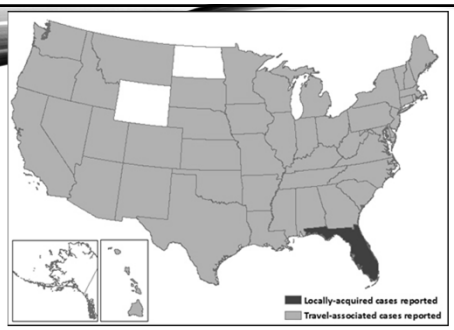
- No direct treatment
- Supportive care only
  - Acetaminophen
  - Ibuprofen
  - Fluids

DENGUE - RESEARCH

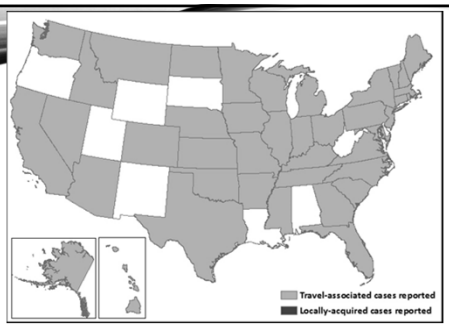
- Largely targeted towards a vaccine
- Also some antivirals
- Not expected to be any new treatments for Dengue in the next 5 years

CHIKUNGUNYA VIRUS

- From Africa and Asia and has been skipping across the Caribbean since 2013
- 2015 – 524 cases in the US from travelers
- 2014 – 2799 cases from travelers
- 2014 – 11 locally acquired cases in Florida



States reporting chikungunya virus disease cases – 2014
(as of February 10, 2015)



States reporting chikungunya virus disease cases – 2015
(as of October 13, 2015)

CHIKUNGUNYA - TRANSMISSION

- Transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes

CHIKUNGUNYA - SYMPTOMS

- Common Symptoms
  - Fever
  - Joint pain
- Other Symptoms
  - Headache
  - Muscle pain
  - Joint swelling
  - Rash
- Usually feel better in a week, but joint pain may last longer

CHIKUNGUNYA - TREATMENT

- No direct treatment
- Supportive care only
  - Acetaminophen
  - Ibuprofen
  - Fluids

CHIKUNGUNYA – FUTURE THERAPIES

- Largely targeted towards a vaccine
  - A promising vaccine is currently in development
- Also some antivirals
  - Nothing real promising

LASSA FEVER

- Acute viral fever common in West Africa
- Only 6 cases in the US since 1969; last in May 2015
- 100,000-300,000 cases in West Africa each year with about 5000 deaths
- Typically infects humans via rodent urine or feces but can be human to humanNo

LASSA FEVER – SYMPTOMS AND TREATMENT

- 80% of patients are asymptomatic
- 20% experience symptoms that are nonspecific at first ("flu-like") and can then begin to effect the GI, cardiac, respiratory and nervous systems
- Treatment is mostly supportive (fluids, reversing hypotension, symptomatic) but can use IV ribavirin
- No commercially available vaccine but research continues

Which of the following is the year when Ebola was first identified?

A. 1893
B. 1954
C. 1976
D. 2013

Which of the following is caused by a virus? (choose all that apply)

A. Ebola
B. Chagas
C. Malaria
D. Chikungunya
E. Dengue
F. Lassa

Which of the following viruses has NOT been transmitted locally within the United States?

A. Ebola
B. Chikungunya
C. Dengue Fever
D. Malaria
E. Chagas
F. All have been transmitted locally

QUESTIONS?

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