ACOI Board Review Course
Hemorrhagic Fever Viruses (VFH) &
Fevers of Unknown Origin (FUO)

MarkAlain Déry, DO, MPH, FACOI
Chief Innovation Officer
Medical Director of HIV and Hepatitis Services
Access Health Louisiana; FQHC
Medical Director AIDS Educational Training Center (AETC)
Medical Director Southern Center for Health Equities

Executive Director;
102.3FM WHIV-LP
Human Rights and Social Justice Radio

madery@whivfm.org

Disclosures

Objectives

At the conclusion of this section, participants;

- By the end of the presentation the attendee will be familiar with the knowledge that persons with Ebola virus disease usually have an abrupt onset of nonspecific symptoms and signs, such as fever, malaise, headache, and myalgias and as the illness progresses, vomiting and diarrhea may develop, often leading to significant fluid loss.
- At the end of the presentation the attendee will be able to comprehend that serologic tests are the main methods for diagnosis of either acute or remote infection by hantaviruses.
- At the end of the presentation the attendee will recognize the minimum diagnostic evaluation for fevers of unknown origin: blood cultures, erythrocyte sedimentation rate or C-reactive protein, serum lactate dehydrogenase, HIV antibody test and viral load, rheumatoid factor, heterophile antibody test, creatine phosphokinase, antinuclear antibodies, tuberculin skin test or interferon-gamma release assay, serum protein electrophoresis, and computed tomography scan of abdomen and chest.

Hemorrhagic Fevers & FUO; VHF Pathogens

PATHOGENS;

- Ebola virus: Africa
- Marburg virus: Africa
- Lassa fever virus: West Africa (most cases in Liberia, Sierra Leone, Guinea and Nigeria)
- New World Arena viridae (Argentine hemorrhagic fever virus, Bolivian hemorrhagic fever virus, Junin hemorrhagic fever virus, etc): South America
- Rift Valley fever virus: Africa, Saudi Arabia
- Yellow fever virus: Africa, tropical Americas
- Omsk hemorrhagic fever virus: Central Asia
- Kyasanur Forest fever virus: India
- Crimean-Congo hemorrhagic fever: Eastern Europe, Africa
- Severe fever with thrombocytopenia syndrome (SFTS): China
- Dengue fever virus

DIAGNOSIS

- Consider risk factors, travel to endemic area and contact with known cases.
- Specimens for viral culture require BSL-4 lab.

Hemorrhagic Fevers & FUO; VHF Clinical

CLINICAL

- Definition: fever + bleeding diathesis caused by infection of a virus listed above.
- Transmission: by animals (including human-human) or insects, but remains incompletely understood for Ebola and Marburg viruses.
- All agents are candidates for bioterrorism.
- Clinical features: fever, severely ill, hemorrhage and thrombocytopenia.
  - Also common:
    - Myalgia
    - Rash
    - Encephalitis
    - Headache
    - Diarrhea, often bloody
    - Abdominal pain
    - Hypotension
    - Conjunctivitis
    - Pharyngitis
    - Elevated LFT's
- Differential diagnosis: influenza, dengue, meningococcemia, malaria, salmonellosis, plague, toxic shock syndrome, hantavirus, HSP, HUS.
- Abdominal presentations may be confused with appendicitis, intersussception.
- Prognosis (mortality): Ebola 20-90%, Marburg 30-60%, Lassa 15-20% (for hospitalized patients, overall 1%), yellow fever 20%.
- Reporting: call immediately to State Health Dept and CDC if case suspected: acute fever < 3 wks duration, severe illness, no alternative dx + unexplained hemorrhage.

Hemorrhagic Fevers & FUO; VHF Clinical

TREATMENT;

- ***Infection Control!!!!***
- Person-person transmission: Ebola, Marburg, Lassa.
- There is NO person-person transmission with Rift Valley, yellow fever, Omsk, Kyasanur Forest.
- No hemorrhagic fever virus (other than Dengue) has ever been acquired in U.S.
- Consider acquisition if within 21 days of travel or bioterrorism event.
- ***Report immediately to public health authorities.***
- Enhanced barrier and airborne precautions until Marburg and Ebola ruled out.
  - Barrier: double glove, impermeable gowns, face shield, goggles, leg and shoe covers.
  - Airborne: N-95 mask or air-purifying respirators (PAPR).
  - If available: negative pressure isolation room w/ 6-12 air exchanges/hr.
- Surveillance of those exposed for febrile disease for 21 days post contact.
  - Laboratory issues:
    - Aerosol risk: perform essential tests only, prefer point-of-care analyzers.

Hemorrhagic Fevers & FUO; VHF Clinical

TREATMENT;

- Environment:
  - Treat all surfaces: household bleach 1:100
  - Cloth: double bag and wash hot cycle w/bleach; autoclave or incinerate.
  - Cadavers: trained personnel, airborne and contact precautions, prompt burial or cremation, no embalming.
- Patient Care
  - Support: IV fluids, mechanical ventilation, dialysis, vasopressors, anti-seizure medications.
  - AVOID: aspirin, NSAIDS.
  - Lassa or Rift Valley Fever:
    - Ribavirin
  - Ebola, Marburg, Yellow fever: no antivirals exist.
- Contacts of Patients
  - Monitor temperature twice daily x 21 days post contact.
  - T >101°F: ribavirin (above oral doses) unless known to be Ebola/Marburg/yellow fever/Omsk/Kyasanur.
  - Vaccines: yellow fever only; not effective post exposure.

Hemorrhagic Fevers & FUO; Hantavirus Microbiology

Hantavirus

MICROBIOLOGY

- Segmented, negative sense RNA virus. Large number of species (23 to date) with more discovered regularly.
- Member of Bunyaviridae, hantaviruses are rodent borne viruses associated with specific reservoirs.
- In the U.S., geographic locales differ:
  - Southeast: deer mice, cotton and rice rats
  - Northeast: white-footed mouse has been associated
  - Transmission to humans through inhalation of aerosolized saliva, urine or feces of reservoir host.
  - **Hantavirus New World:** (e.g., Sin Nombre virus) known to cause hantavirus pulmonary syndrome (HPS)

Hemorrhagic Fevers & FUO; Hantavirus Clinical

CLINICAL

- In U.S., most common pathogenic Hantavirus is Sin Nombre virus, cause of acute cardiopulmonary syndrome; mostly in southwestern U.S. (four corner states, mainly Arizona, Colorado); also elsewhere (Vermont, Central and South America).
- Initially manifests as undifferentiated febrile illness, with fulminant progression to ARDS-like picture typically in previously healthy young adults.
- Early symptoms are non-specific.
  - Fever, headache, myalgia, GI upset, dizziness, chills.
  - Then cardiopulmonary sxs develop, 4-10d after onset (d5 = average).
  - Most characteristic is thrombocytopenia, less so is hemoconcentration.
  - WBC: leukocytosis common w/ left shift including bandemia and atypical lymphocytes.
  - DIC associated with severe cases.
  - Rodent infestation of home remains leading risk factor, especially cleaning uninhabited trailer, cabin or residence in SW U.S.
  - High case fatality rate (30-50%).
  - September 2012: 9 cases described acquired within Yosemite National Park, California.

Hemorrhagic Fevers & FUO; Hantavirus Diagnosis and Treatment

DIAGNOSIS:
- Serology (hantavirus-specific (HS) IgM or rising titers of HS IgG)
- PCR HS RNA by PCR
- Immunohistochemistry: HS antigen on tissue
- Culture: rarely viral isolation

TREATMENT;
- Supportive therapy
  - Early recognition important for directing intensive care.
  - Management of fluid status critical to reduce risk of respiratory failure.
  - HPS: repeat CBC and chemistry profile q 8-12 h. Rising HCT or falling albumin may point to pulmonary edema/fluid shift to lung from circulation.
  - ICU/supportive care is only directed therapy.

PREVENTION
- Avoid exposure to rodents or their droppings (home, workplace or campsites).
  - Rodent control:
    - Seal holes in home.
    - Trap rodents.
    - Keep food in containers, clean up any food debris.

Hemorrhagic Fevers & FUO; FUO Definition

Fever of Unknown Origin (FUO)

DEFINITION;

- Classic definition: (Petersdorf and Beson, Medicine, 1961)
  - Fever ≥ 38.3°C
  - Illness > 3 weeks
  - Negative evaluation with hospital workup for ≥ 1 week
- Modern definition:
  - Temperature > 38.3°C for > 3 wks duration without a diagnosis despite 2 outpt visits or 3 hospital days

Hemorrhagic Fevers & FUO; FUO Pathogens/Causes

PATHOGENS/CAUSES

- Categories based on classical criteria ("classical FUO"): infection 36%, inflammatory/rheumatological 35%, malignancy 15%, miscellaneous 20%.
  - Special subsets:
    - Nosocomial or postoperative: drug fever, phlebitis, pulmonary embolism or infection related to surgery
    - AIDS: (CD4 < 200 cells/mL): MAC, CMV, TB, lymphoma, PCP
    - Elderly: malignancy, temporal arteritis/polymyalgia rheumatica
    - Fever >1yr: lymphoma, normal variant (benign hyperthermia or FUO chronic without specific diagnosis), factitious, granulomatous hepatitis
    - Infectious: TB, endocarditis, Q fever, brucellosis, subacute endocarditis, intra-abdominal or pelvic abscess, Epstein-Barr virus, cat-scratch disease
    - Inflammatory conditions: adult Still's disease, giant cell arteritis, systemic lupus, arteritis, Kikuchi disease, sarcoidosis
    - Malignancy: lymphoma, hypernephroma, pre-leukemia, myeloproliferative disorders, multiple myeloma, hepatoma, liver metastases
    - Miscellaneous: drug fever, pulmonary emboli, familial Mediterranean fever (FMF), periodic fever, giant cell arteritis (GCA)
    - Other: factitious fever, fraudulent fever, normal temperature variant, tumor fever, hereditary (periodic fever), pulmonary emboli
    - Returning travelers (malaria, typhoid fever, influenza)

Hemorrhagic Fevers & FUO; FUO Clinical

CLINICAL;

- General Comments
  - Verify fever: defined as core temperature >38°C (100.4°F, some use 38.3°C)
    - Normal temperature:
      - Median 36.8°C (98.2°F), range +/- 0.9°F (0.5°C)
      - Peak 4-6 PM
      - Nadir 6 AM
    - Examine thoroughly including mouth, temporal arteries (age >50), abdomen, spleen, liver, skin, lymph nodes.
    - Labs (initial): CBC with differential, CRP, ESR, procalcitonin, chemistry panel, chest x-ray, U/A, ANA, blood culture x 3, HIV serology.
    - Imaging: CT chest/abdomen/pelvis.

Hemorrhagic Fevers & FUO; FUO Clinical

CLINICAL;

- Infectious diseases
  - Abdominal abscess: CT scan, abx + drainage.
  - TB or atypical mycobacteria: PPD or IGRA, chest x-ray, AFB sputum cx, LP, liver bx, marrow bx - w/ granulomas.
- Culture-negative endocarditis: consider HACEK organisms, nutritionally-variant streptococci; *Bartonella*, Q fever (Coxiella burnetii, *Legionella*, *Brucella* (serology), fungi.
- DX: echo (TEE), abx-empiric.
- Mononucleosis syndromes: ~80% EBV (atypical lymphocytes + Mono spot); other causes include CMV, toxoplasmosis, acute HIV.

Hemorrhagic Fevers & FUO;
FUO Clinical

CLINICAL;

- Granulomatous and collagen vascular diseases
  - Temporal arteritis: age > 50, ESR > 50, wt loss, PMR sx, vision sx.
  - Dx: temporal or occipital artery bx.
    - Treatment: prednisone 60mg/d ASAP to avoid blindness while getting temporal artery bxp within one week to avoid prednisone rendering biopsy as uninformative.
  - Polymyalgia rheumatica: age > 50, ESR > 50, pain (neck, shoulder, pelvis).
    - Clinical dx.
    - Treatment: prednisone 20mg/d (dramatic abatement of sx w/i 1-2d is supportive of diagnosis).
- Still's disease: arthralgia/arthritis, faint fleeting rash, LN, leukocytosis, anemia, ANA negative, remitting fever, high ESR/CRP, elevated ferritin.
  - Treatment: ASA/NSAID or corticosteroid responsive.
  - Sarcoid: chest x-ray, bxp of tissue - documenting usually non-caseating granuloma. R/O TB, lymphoma.
  - Crohn's dz: dx by endoscopy + bxp.
  - Granulomatous hepatitis: ESR > 50, increased alk phos, wt loss. Dx: liver bxp, r/o TB. Rx steroids.

Hemorrhagic Fevers & FUO;
FUO Clinical

CLINICAL;

- Tumors/miscellaneous
  - "Omas:" lymphoma, myeloma, hypernephroma. DX: CT scan, serum immunoglobulins, SPEP/UPEP, biopsies.
  - Hodgkins/non-Hodgkins lymphoma: intermittent fever, LN, liver/spleen enlarged, naproxen response. Dx: LN, liver or marrow bx.
  - Solid tissue tumors: CT scan, LFTs for liver mets. Dx: bx.
  - Drug fever: looks well for temperature with relative bradycardia. Occurs typically 1-3 wks post start of drug (phenytoin, sulfa, beta-lactam, barbiturate, clindamycin, dapsone, amB). D/C = typical response w/i 48 hrs (exceptions, severe drug fever with rash syndromes e.g., DRESS, Stevens-Johnson Syndrome, etc).
  - Pulmonary embolism: increased respirations or dyspnea, edema, atelectasis or effusion. Dx V/Q scan or angiography (chronic PE not well dx by CT method). Rx: anticoagulation.
  - Familial Mediterranean Fever: Jews, Armenians, Turks. Attacks of fever & pain w/ no alternative cause +/- serositis, amyloidosis. Rx: colchicine.
  - Self-induced: fraudulent behavior, may see polymicrobial bacteremia, often young adult; otherwise appears healthy.
  - Factitious: deceit in often healthy young adult, negative labs, ESR nl. No diurnal temp change, urine temp nl. Rx: confrontation.

Hemorrhagic Fevers & FUO;
FUO Clinical

OTHER INFORMATION

- Most common diagnoses:
  - ID: TB, endocarditis
  - Inflammatory disorders: Stills disease, GCA/PMR, vasculitis.
  - Tumor: lymphoma
  - Other: granulomatous hepatitis, drug fever, PE, FMF, factitious
  - No diagnosis found in 20-50%. Prognosis for them is generally good.
  - Episodic FUO: explanations only found in a minority. Often a benign process.