Emerging Infections

David V. Condoluci, DO., F.A.C.O.I.
Declaratives

- I have no conflicts of interest.
- I do not speak for any companies
- I have no grants other than Ryan White and AETC from the federal government
Objectives

- To identify the emerging infectious diseases facing us today
- To show how the landscape is changing in regards to new pathogens of concern
- To give insight into presentation and treatment of these emerging pathogens
Emerging Infectious Disease?

“this time I will send the full force of my **plagues** against you and against your officials and your people”

*Exodus 9:14*
New Emerging Infectious Diseases

- Zika virus
- EBOLA
- TB
- West Nile Virus
- Meningococcal strains
- Drug resistant microorganisms
- MERS-CoV
- Measles
- Influenza
Viral Hemorrhagic Fever (VHF)

**Syndromes**

**INFLUENZA**

**PULMONARY**

**HEPATIC**

**NEUROLOGICAL**

**DERMATOLOGICAL**

- Intracranial Hemorrhage
- Conjunctival hemorrhage
- Confusion
- Facial flushing
- Capillary Fragility
- Disseminated Intravascular Coagulation
- Shock
- Pneumonia (Hanta)
- Jaundice LFT (RVF, MHF, EHF, YF)
- Hematemesis
- Melena
- Renal failure (HFRS)
- Thrombocytopenia
- Leukopenia

**Early Symptoms**

- Headache
- Deafness
- Visual deficits (RVF)
- Epistaxis
- Sore throat
- Black vomit (YF)
- Nausea, Vomiting
- Abdominal pain
- Diarrhea
- Myalgia
- Petechiae
- Purpura
- Ecchymosis
- Macular rash (MHF, EHF)
- Non-dependent swelling

**Delayed Symptoms**

- Fever, Malaise, Prostration
Viral Hemorrhagic Fever (VHF) low incidence high--consequence

Bunyaviridae
Hantavirus (HFRS)
Rift Valley Fever (RVF)
Congo-Crimean (CCHF)

Arenaviridae
Lassa Fever (LF)

Filoviridae
Congo, Sudan, Uganda
Marburg (MHF)
Ebola (EHF)

Flaviviridae
Yellow Fever (YF)
Dengue (DHF)
EBOLA
Why Ebola is so dangerous

Health care workers are among those most at risk of catching Ebola
Classification of Ebola virus

• Order Mononegavirales
  • Enveloped, nonsegmented, negative strand RNA viruses

• Family Filoviridae contains 3 genera:
  • Ebolavirus (1976)
  • Marburgvirus – Lake Victoria marburgvirus (1967)
  • Cuevaivirus – Lloviu virus (bats, Spain, 2002)
Fig. 1: Air traffic connections from West African countries to the rest of the world

Air traffic connections from West African countries to the rest of the world. Guinea, Liberia, and Sierra Leone are not well connected outside the region. Nigeria, in contrast, being the most populous country in West Africa with more than 166 million people, is well connected to the rest of world. For historical reasons, all these countries have the strongest ties with European countries.
Reservoir and transmission to humans

- Fruit bats reservoir of virus - Drop partially eaten fruits
- Bats infect chimpanzees, gorillas, forest antelopes, porcupines
- Humans handle and eat bush meat (bats, chimpanzees, gorillas)
- Infected human passes from person to person

Centers for Disease Control and Prevention; Virus Ecology Graphic
Pathogenesis - transmission

- Fastest incubation period has been reported associated with needle stick injury.
- Viral load may correlate with disease severity and survival.
- This is NOT an airborne disease. Thus the pulmonary disease is hemorrhage and ARDS associated with severe sepsis.
Pathogenesis - how does Ebola cause disease?

- Virus enters the body via infected blood/body fluid in contact with a mucosal surface or a break in intact skin.
- Virus replicates preferentially in monocytes/macrophages and dendritic cells which facilitate dissemination of the virus throughout the body via lymphatic system.
- Other cells are secondarily infected and there is rapid viral growth in hepatocytes, endothelial and epithelial tissues.
- There is strong cytokine/inflammatory mediator release of TNF-a and inflammatory cascade.
Pathogenesis - inflammatory response

- Leads to endothelial damage, increased vascular permeability and shock.
- This results in the end organ damage and multi-organ dysfunction
- Diffuse intravascular coagulopathy (DIC) with platelet and coagulation factor consumption which leads to hemorrhage.
- IgM starts forming in 2 day and IgG in 5-8 days post infection. Immunologic response correlates with survival.
- Thus the observation that those who live >1 week are more likely to survive.
Clinical Manifestations

- Incubation period 8-10 days (range 2-21)
- Sudden onset of Fever \(>38.6^\circ\)C
- Flu-like symptoms: chills, myalgias, and malaise, sore throat
- Nausea, vomiting, abdominal pain, diarrhea
- Respiratory symptoms of chest pain, shortness of breath and cough
- CNS symptoms: Headache, confusion and coma
Clinical Manifestations

- Rash occurs around day 5
- Hypotension, peripheral edema
- Bleeding manifestations develop in >50% (internal/external)
- Can vary from petechiae & easy bruising, to mucosal hemorrhage, uncontrolled bleeding and massive GI blood loss
- Multi-organ dysfunction: kidneys and Liver
- Laboratory abnormalities
  - Thrombocytopenia and leukopenia
  - Elevated transaminases (AST > ALT), amylase, D-dimer
  - Reduced albumin
Immunity and Survival

- Treatment is supportive care
- IgG response appears to be protective
- Survivors may have persistent high antibody titres and associated sequelae of hepatitis, uveitis, muscle weakness etc.
- Previous observation was that serum from an Ebola survivor was therapeutic
- Anecdotal reports of Mab therapy being successful
- **Caution**, in a disease with 50% survival, any anecdotal observation can be a chance event
- It does support the potential role of vaccination
Context for outbreak

- Widespread on multiple fronts
- Affected large cities
- Weak and fragile infrastructure
- Lack of knowledge of the disease
- Distrust of government and foreigners
- Not seeking health care
- Social rituals / burial rituals
- Delayed response; more resources needed
Impact on social determinants of health

- Trading, industry, agriculture, tourism
- Worsening poverty
- Hunger
- Orphans
- Stigma
- School closures
- Other diseases not being treated
- Lack of preventive care: prenatal care, vaccination
Key Ebola Virus Disease Facts

- Only spread by direct contact with blood and body fluids; not airborne
- Incubation 2-21 days; usually 8-10 days
- Only infectious when symptomatic
- Increasingly infectious as get sicker
IPAC Practices for EVD: Droplet + Contact Precautions

• Patient accommodation:
  • Single room with dedicated bathroom (minimum requirement); door closed
  • consider use of an isolation room that has an anteroom for donning or doffing PPE

• PPE for all staff entering the room:
  • fluid-resistant, long-sleeved, cuffed gown
  • gloves
  • full face protection (face shield)
  • surgical or procedure mask

• Maintain log of all individuals entering the room; only essential people should enter the room
### Key Components of Standard, Contact, and Droplet Precautions Recommended for Prevention of EHF Transmission in U.S. Hospitals

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Placement</td>
<td>• Single patient room (containing a private bathroom) with the door closed</td>
<td>• Consider posting personnel at the patient’s door to ensure appropriate and consistent use of PPE by all persons entering the patient room</td>
</tr>
<tr>
<td></td>
<td>• Facilities should maintain a log of all persons entering the patient’s room</td>
<td></td>
</tr>
<tr>
<td>Personal Protective Equipment (PPE)</td>
<td>• All persons entering the patient room should wear at least:</td>
<td>• Recommended PPE should be worn by HCP upon entry into patient rooms or care areas. Upon exit from the patient room or care area, PPE should be carefully removed without contaminating one’s eyes, mucous membranes, or clothing with potentially infectious materials, and either</td>
</tr>
<tr>
<td></td>
<td>◦ Gloves</td>
<td>- Discarded, or</td>
</tr>
<tr>
<td></td>
<td>◦ Gown (fluid resistant or impermeable)</td>
<td>- For re-useable PPE, cleaned and disinfected according to the manufacturer’s reprocessing instructions and hospital policies.</td>
</tr>
<tr>
<td></td>
<td>◦ Eye protection (goggles or face shield)</td>
<td>• Instructions for donning and removing PPE have been published</td>
</tr>
<tr>
<td></td>
<td>◦ Facemask</td>
<td>• Hand hygiene should be performed immediately after removal of PPE</td>
</tr>
<tr>
<td></td>
<td>• Additional PPE might be required in certain situations (e.g., copious amounts of blood, other body fluids, vomit, or feces present in the environment), including but not limited to:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>◦ Double gloving</td>
<td></td>
</tr>
<tr>
<td></td>
<td>◦ Disposable shoe covers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>◦ Leg coverings</td>
<td></td>
</tr>
<tr>
<td>Patient Care Equipment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dedicated medical equipment (preferably disposable, when possible) should be used for the provision of patient care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• All non-dedicated, non-disposable medical equipment used for patient care should be cleaned and disinfected according to manufacturer’s instructions and hospital policies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Care Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Limit the use of needles and other sharps as much as possible</td>
</tr>
<tr>
<td>• Phlebotomy, procedures, and laboratory testing should be limited to the minimum necessary for essential diagnostic evaluation and medical care</td>
</tr>
<tr>
<td>• All needles and sharps should be handled with extreme care and disposed in puncture-proof, sealed containers</td>
</tr>
</tbody>
</table>
August 8, 2014
Hello Everyone,

While Ebola is primarily limited to West Africa, the disease is not contained. International travel is not restricted, and we need to have a plan in place in the event Ebola reaches our doorsteps.

- **It is very important from the get-go at triage to obtain a travel history to West Africa.**
- **Symptoms of Ebola include fever, headache, diarrhea, and vomiting blood.**
- **Ebola is incredibly infectious!**
- **As soon as there is any suspicion, immediately place the patient in a negative pressure room (see the designated rooms below), with a dedicated bedside commode. Restrict visitors, and notify infection control and infectious disease.**
- **Proper and extensive PPE — personal protective eyewear/mask, gown, gloves, footwear are recommended, and we recommend being covered from head to toe and double-gloved.**
- **Hand hygiene and glove use must be employed at all times. Please note that infections have spread with Ebola when there has been a break in infection control.**
- **In the event the ER has a suspected Ebola patient, they must use one of the ER rooms designated below with the door closed. They will then triage to the ICU or floor in one of the designated rooms.**

Please read through this CDC link: [http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html](http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html)

In the event of any suspicion of an active Ebola case, immediately notify us, **24/7**, by calling us at:
- **Dr. Cindy Hou, 609-405-114 (cell)**
- **Dr. David Condoluci, 609-405-5128 (cell)**
- **Marianne Kraemer, 609-313-3460 (cell)**

It is important that we have everyone’s safety in mind — our patients, ourselves, and the ones we love. In the event that we encounter a patient with a suspected case, all communication to the news outlets will be handled by our media department. Remember in all of this, HIPPA still must be maintained.

Thank you,
Dr. Hou
Dengue Fever
Dengue

- Dengue is found mainly in tropical and subtropical areas of the world
- Present in more than 100 countries
Dengue fever and dengue haemorrhagic fever (DHF) are viral diseases transmitted by *Aedes* mosquitoes, usually *Aedes aegypti*. DHF can be fatal in 20% without supportive treatment. There are four types of this virus (serotypes 1 to 4) and are closely related to one another. There is good evidence that sequential infection increases the risk of more serious disease resulting in DHF.
Dengue

- Classic Dengue
- DHF without shock
- DHF with shock
Dengue

- Incubation period of 3-10 days
- Sudden onset with chills and high fever
- Reddened eyes
- Intense muscle and joint pain
- Flushing or pale pink rash over face and then disappears
- Glands in neck and groin swollen
- Fever 2-4 D, recovery complete
DHF

- Due to double infection triggering immune response
- Headache and high fever
- Petechial rash
- Bleeding of gums and nose
- Black stools and bruising
- Can be life threatening
Dengue

- No specific treatment
- Supportive care
- Fluid resuscitation
- No immunization
- Good public health measures to prevent
Chikungunya virus disease

- Mosquito-borne viral disease characterized by acute onset of fever and severe polyarthralgia
- Often occurs in large outbreaks with high attack rates
- Outbreaks have occurred in countries in Africa, Asia, Europe, and the Indian and Pacific Oceans
- In 2013, first locally-acquired cases in the Americas reported on islands in the Caribbean
Chikungunya virus in the Americas*

- Seven Caribbean countries have reported locally-acquired cases
- >1,000 laboratory-confirmed cases have been reported
- Virus expected to spread to new areas

*As of February 10, 2014
Mosquito vectors

- Predominantly *Aedes aegypti* and *Aedes albopictus*
- Same mosquitoes that transmit dengue
- Widely distributed throughout Americas
- Aggressive daytime biters

![Image of Aedes aegypti](image1) ![Image of Aedes albopictus](image2)
Chikungunya virus infection

- Majority (72%–97%) of infected people develop clinical symptoms
- Incubation period usually 3–7 days (range 1–12 days)
- Primary clinical symptoms are fever and polyarthralgia
Fever and polyarthralgia

- Fever
  - Abrupt onset
  - Typically ≥39.0°C (≥102.2°F)

- Joint pain
  - Often severe and debilitating
  - Involves multiple joints
  - Usually bilateral and symmetric
  - Most common in hands and feet
Other clinical signs and symptoms

- Headache
- Myalgia
- Arthritis
- Conjunctivitis
- Nausea/vomiting
- Maculopapular rash
Clinical laboratory findings

- Lymphopenia
- Thrombocytopenia
- Elevated creatinine
- Elevated hepatic transaminases
Clinical outcomes

- Acute symptoms typically resolve in 7–10 days
- Mortality is rare; occurs mostly in older adults
- Some patients have relapse of rheumatologic symptoms* in the months following acute illness
- Studies report variable proportions of patients with persistent joint pains for months or years

*Polyarthralgia, polyarthritis, tenosynovitis, Raynaud’s syndrome
<table>
<thead>
<tr>
<th>Diagnostic assay</th>
<th>Days post-illness onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral culture</td>
<td>≤3 days</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>≤8 days</td>
</tr>
<tr>
<td>IgM antibody tests</td>
<td>≥4 days</td>
</tr>
</tbody>
</table>
Treatment

- No specific antiviral therapy
- Supportive care with rest and fluids
- Non-steroidal anti-inflammatory drugs (NSAIDs) for acute fever and pain*
- Persistent joint pain may benefit from use of NSAIDs, corticosteroids, or physiotherapy

*Aspirin use is discouraged due to a theoretical risk of hemorrhage or Reye syndrome
Zika Virus

- Single stranded RNA Virus
- Genus *Flavivirus*, Family *Flaviviridae*
- Closely related to dengue, yellow fever, Japanese encephalitis and West Nile viruses
- Transmitted to humans primarily by *Aedes (Stegomyia)* species mosquitoes
Zika Virus Vectors: 
Aedes Mosquitoes

- *Aedes* species mosquitoes
  - *Ae aegypti* more efficient vectors for humans
  - *Ae albopictus*

- Also transmit dengue and chikungunya viruses
- Lay eggs in domestic water-holding containers
- Live in and around households
- Aggressive daytime biters
Aedes aegypti and Aedes albopictus Mosquitoes: Geographic Distribution in the United States
Other Modes of Transmission

- Maternal-fetal
  - Intrauterine
  - Perinatal
- Other
  - Sexual
  - Blood transfusion
  - Laboratory exposure
- Theoretical
  - Organ or tissue transplantation
  - Breast milk
Zika Virus:
Countries and Territories with Active Zika Virus Transmission

as of January 23, 2016
Zika Virus in the Americas

- In May 2015, the first locally-acquired cases in the Americas were reported in Brazil.
- Currently, outbreaks are occurring in many countries or territories in the Americas, including the Commonwealth of Puerto Rico and the U.S. Virgin Islands.
- Spread to other countries likely.
Zika Virus Incidence and Attack Rates

- Infection rate: 73% (95%CI 68–77)
- Symptomatic attack rate among infected: 18% (95%CI 10–27)
- All age groups affected
- Adults more likely to present for medical care
- No severe disease, hospitalizations, or deaths

Note: Rates based on serosurvey on Yap Island, 2007 (population 7,391)
# ZIKA

Reported Clinical Symptoms Among Confirmed Zika Virus Disease Cases

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or papular rash</td>
<td>28</td>
<td>90%</td>
</tr>
<tr>
<td>Subjective fever</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>17</td>
<td>55%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15</td>
<td>48%</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>45%</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>12</td>
<td>39%</td>
</tr>
<tr>
<td>Edema</td>
<td>6</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>

Yap Island, 2007
Zika Virus Clinical Disease Course and Outcomes

- Clinical illness usually mild
- Symptoms last several days to a week.
- Severe disease requiring hospitalization uncommon
- Fatalities are rare
- Guillain-Barré syndrome reported in patients following suspected Zika virus infection
  - Relationship to Zika virus infection is not known
Zika Virus and Microcephaly in Brazil

- Reports of a substantial increase in number of babies born with microcephaly in 2015 in Brazil; true baseline unknown
  - Zika virus infection identified in several infants born with microcephaly (including deaths) and in early fetal losses
  - Some of the infants with microcephaly have tested negative for Zika virus
- Incidence of microcephaly among fetuses with congenital Zika infection is unknown
Distinguishing Zika from Dengue and Chikungunya

- Dengue and chikungunya viruses transmitted by same mosquitoes with similar ecology
- Dengue and chikungunya can circulate in same area and rarely cause co-infections
- Diseases have similar clinical features
- Important to rule out dengue, as proper clinical management can improve outcome

### Clinical Features:
#### Zika Virus Compared to Dengue and Chikungunya

<table>
<thead>
<tr>
<th>Features</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Diagnostic Testing for Zika Virus

- Reverse transcriptase-polymerase chain reaction (RT-PCR) for viral RNA in serum collected $\leq 7$ days after illness onset
- Serology for IgM and neutralizing antibodies in serum collected $\geq 4$ days after illness onset
- Plaque reduction neutralization test (PRNT) for $\geq 4$-fold rise in virus-specific neutralizing antibodies in paired sera
- Immunohistochemical (IHC) staining for viral antigens or RT-PCR on fixed tissues
Serology Cross-Reactions with Other Flaviviruses

- Zika virus serology (IgM) can be positive due to antibodies against related flaviviruses (e.g., dengue and yellow fever viruses)
- Neutralizing antibody testing may discriminate between cross-reacting antibodies in primary flavivirus infections
- Difficult to distinguish infecting virus in people previously infected with or vaccinated against a related flavivirus
- Healthcare providers should work with state and local health departments to ensure test results are interpreted correctly
ZIKA

Initial Assessment and Treatment

- No specific antiviral therapy
- Treatment is supportive (i.e., rest, fluids, analgesics, antipyretics)
- Suspected Zika virus infections should be evaluated and managed for possible dengue or chikungunya virus infections
- Aspirin and other NSAIDs should be avoided until dengue can be ruled out to reduce the risk of hemorrhage
Zika Virus Disease Surveillance

- Consider in travelers with acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis within 2 weeks after return
- Inform and evaluate women who traveled to areas with Zika virus transmission while they were pregnant
- Evaluate fetuses/infants of women infected during pregnancy for possible congenital infection and microcephaly
- Be aware of possible local transmission in areas where *Aedes* species mosquitoes are active
Zika Virus Preventive Measures

- No vaccine or medication to prevent infection or disease
- Primary prevention measure is to reduce mosquito exposure
- Pregnant women should consider postponing travel to areas with ongoing Zika virus outbreaks
- Protect infected people from mosquito exposure during first week of illness to prevent further transmission
Conclusions

- Emerging infectious diseases are omnipotent and will continue to command attention.
  - EID’s are most deleterious in 1) developing nations and 2) among children, the elderly, females, and those with weakened immune systems
- EID’s are controllable!
- It is the responsibility of the global community to continue to develop / refine public health infrastructures to deal with burgeoning crises.
- Initiatives must be developed in order to overcome social, religions, and regional barriers to prevention and control.
— AND NOW IT’S TIME TO PLAY OUR EVER-POPULAR GAME...

PANIC OF THE WEEK

THE MEDIA

MAD COW DISEASE

TERRORISM ALERT

SARS

MUMMIFIED CORPSES

PHONY DRUGS @X

WMD

GASOLINE SHORTAGE

AIDS SHORTAGE
FUO

David V. Condoluci, DO., F.A.C.O.I.
Objectives

• To define what is an FUO
• To show how the landscape has changed for the causes of FUO
• To review the workup and potential treatment of FUO presentations
Fever of unknown origin (FUO) was defined in 1961 by Petersdorf and Beeson as the following: (1) a temperature greater than 38.3°C (101°F) on several occasions, (2) more than 3 weeks' duration of illness, and (3) failure to reach a diagnosis despite 1 week of inpatient investigation.[1, 2]
FUO

• Landscape has changed the old definition

• Early detection of tumors and laboratory tests make one time obscure causes more readily identified today
FUO

• Generally long term FUO’s that have little evidence of serious systemic disease generally resolve.

• The FUO that is difficult is the one that is prolonged, systemically causing signs of serious illness and after a serious workup remain elusive. That is the focus of this talk.
Fever not FUO

• HAI (respiratory, UTI, wound, catheter, sinusitis, C.difficile)
• Neutropenic (Infections-bacterial, viral, fungal, TB and malignancy)
• HIV (infections, drugs, fever)
• Generally these should be detectable by studies
Contemporary FUO

• Illness greater than three weeks duration
• Temp greater than 38.3 degrees with lab signs of inflammation on several occasions
• No diagnosis after initial investigation
• Exclusion of HAI, and immunocompromised such as HIV
FUO

- **Comprehensive history** (including travel history, risk for venereal diseases, hobbies, pet animals and birds, etc.)
- **Comprehensive physical examination** (including temporal arteries, rectal digital examination, etc.)
- **Routine blood tests** (CBC including differential, ESR or CRP, electrolytes, renal and hepatic tests, CK and LDH)
- **Microscopic urinalysis**
- **Cultures of blood, urine other normally sterile compartments if indicated, e.g. joints, pleura, cerebrospinal fluid**
- **Chest radiograph**

D Knockaert J Int med 2003;253:263
FUO

- Abdominal and or chest CT
- Antinuclear and antineutrophilic cytoplasmic antibodies, rheumatoid factor
- Tuberculin skin test
- Serological tests directed by local epidemiological data
- Further evaluation directed by abnormalities detected by above test

D Knockaert J Int med 2003;253:263
FUO

- HIV antibodies depending on detailed history
- CMV-IgM and EBV serology in case of abnormal differential WBC count
- Echocardiography in case of cardiac murmur
FUO

• FUO is not simple
• It can be one of over two hundred different causes
• Clinically you must do a careful detailed evaluation sometimes over and over again using all the clinical skills available
FUO Menu

- Abscesses
- Tuberculosis
- Urinary tract infections
- Endocarditis
- Hepatobiliary infections
- Osteomyelitis
- Rickettsia
- Chlamydia
- Systemic bacterial illnesses
- Spirochetal diseases
- HIV

- Fungal infections
- Parasitic infections
- Lymphomas/Leukemia
- Solid tumors
- Malignant histiocytosis
- Collagen vascular
- Sarcoidosis
- Regional enteritis
- Granulomatous hepatitis
- Drug fever
- Endocrine disorders
- Peripheral pulmonary emboli
FUO Menu

• Factitious fever
• Giant cell arteritis (GCA)
• Polymyalgia rheumatica (PMR)
• Polyarteritis nodosa (PAN)
14 disorders ~ 2/3 of the diagnoses

1. Infections:
   - Endocarditis
   - Tuberculosis
   - Abdominal abscesses
   - EBV/CMV infections

Most Common Causes

2. Malignancies:
   - Lymphoma
   - Leukemia

3. Non-infectious inflammatory disorders
   - Adult-onset Still disease
   - Systemic lupus erythematosus
   - Polymyalgia rheumatica – giant cell arteritis
   - Sarcoidosis
   - Crohn disease

Most Common Causes

4. Miscellaneous disorders
   Habitual hyperthermia
   Drug fever
   Subacute thyroiditis

FUO

• Abscesses - W/U should be able to identify
• Tuberculosis - skin testing, quatiferon AU, tissue and culture
• Urinary tract infections
• Endocarditis - Mainly CNE-causes
• Hepatobiliary infections
• Osteomyelitis
• Rickettsia - lymes, erlichia, babesia, relapsing fever
FUO

• Chlamydia
• Systemic bacterial illnesses-Brucella
• Spirochetal diseases-RBF, Lymes, syphilis
• HIV
• Fungal infections-blasto, histo, cocci
• Parasitic infections-toxo, trypan, leishman
FUO

• Lymphoma’s
• Leukemia's
• Solid tumors-renal cell,
• Malignant histiocytosis
• Collagen vascular and autoimmune diseases
• Sarcoidosis
• Regional enteritis-Chrons
• Granulomatous hepatitis
FUO Hx

• Family history
• Immunization status
• Occupational history
• Travel history
• Nutrition (including consumption of dairy products)
• Drug history (over-the-counter medications, prescription medications, illicit substances)
• Sexual history
• Recreational habits
• Animal contacts (including possible exposure to ticks and other vectors)
Prioritize

- Age matters
- Where you have been matters
- Pattern could matter but not diagnostic
- Time frame usually infections, and malignancy will show over time with careful observation
FUO-Px

- Needs to be complete and repeated
- Relative bradycardia
- Makes sure it is fever with documentation
- Pattern of fever
- Rashes
- Lymph node stations
R/O Common 3

- Infectious
- Malignancy
- Inflammatory
• Abdominal Abscess
• Actinomycosis
• Acute Lymphoblastic Leukemia
• Acute Myelogenous Leukemia
• Adenoviruses
• Adrenal Carcinoma
• Adrenal Insufficiency
• Amebiasis
• Amebic Hepatic Abscesses
• Atrial Myxoma
• Atypical Mycobacterial Infection
• Bacillary Angiomatosis
• Bacteroides Infection
• Bartonellosis
• Blastomycosis
• California Encephalitis
• Campylobacter Infections
• Candidiasis
• Carcinoid Tumor, Intestinal
• C burnetii infection
• Chagas Disease (American Trypanosomiasis)
FUO-Diff. Dx

• Cholangitis
• Cholecystitis
• Choledocholithiasis
• Chronic Bacterial Prostatitis
• Chronic LL
• Chronic Mesenteric Ischemia
• Chronic ML
• Clostridia necrotizing fasciitis
• Colon Cancer, Adenocarcinoma
• Coxsackie viruses
• Cryptococcosis

• Cytomegalovirus Colitis
• Dengue Fever
• Diabetic Ulcers
• Drug Fever
• Eastern Equine Encephalitis
• Echoviruses
• Emphysematous Pyelonephritis
• Empyema, Gallbladder
• Empyema, Pleuropulmonary
• Enteroviruses
• Eosinophilic Pneumonia
• Eosinophilic Toxocariasis
FUO-Diff. Dx

• Epididymitis
• Epidural *Abscess*
• Erythema Multiforme (Stevens-Johnson Syndrome)
• Factitious Fever
• Gallbladder Gangrene
• Gastroenteritis, Viral
• *Giardiasis*
• Graves Disease
• Hairy Cell *Leukemia*
• Hepatitis A-E
• Hepatoma
• Herpes Simplex

• Histoplasmosis
• HIV
• Human Herpesvirus Type 6
• Hypersensitivity Pneumonitis
• Hyperthyroidism
• Inflammatory Bowel Disease
• Intra-abdominal Sepsis
• Japanese Encephalitis
• Kikuchi Disease
• Legionnaires Disease
• Leishmaniasis
FUO-Diff. Dx

- Leishmaniasis
- Leptospirosis
- Leukocytoclastic Vasculitis
- Libman-Sacks Endocarditis
- Listeria Monocytogenes
- Liver Abscess
- Lung Abscess
- Lymphocytic Choriomeningitis
- Lyssavirus Infection
- Malaria
- Malignant histiocytosis
- Mastocytosis, Systemic
- Mediterranean Fever, Familial
- Mediterranean Spotted Fever
- Meningococcemia
- Miliary Tuberculosis
- Mucormycosis
- Mycoplasma Infections
- Naegleria Infection
- Neuroleptic Malignant Syndrome
- Nocardiosis
FUO-Diff. DX

- Nonarticular Rheum
- Nonbacterial Prostatitis
- Norwalk Virus
- Onchocerciasis
- Osteomyelitis
- Pancreatitis, Acute
- Pelvic Inflammatory Disease
- Pericholangitis
- Pharyngitis, Viral
- Pneumonia, Viral
- Prostatic Abscess
- Psittacosis

- Q Fever
- Rat-bite Fever (S minor)
- Rhinocerebral Phycomycosis
- Sphenoid Sinusitis
- Thrombophlebitis
- Trypanosoma Infection
FUO-W/U

- Routine labs
- Cultures
- Serologies
- CT and/or MRI
- Endoscopic studies as appropriate
- Radio nucleotide studies
- Bx
FUO-RX

• Treatment directed at cause
• Close follow up
• Consultation as appropriate
• Eventually the fever will resolve without identification of cause or it will progress making the cause identifiable and hopefully treatable
Thank You

• Reference: Fever of Unknown Origin
• Author: Kirk M Chan-Tack, MD; Chief Editor: Burke A Cunha, MD E-Medicine