Difficult to Diagnose Infectious Diseases

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Disclosures

- I have no financial relationships to disclose.
- I will not discuss off-label use and/or investigational use in my presentation.
- Slides provided by various sources including DHHS, CDC, and Arizona Department of Health

Oral Lesions

- A 35 year old man with a history of asthma was seen in the clinic. At the time of visit he complained of having white plaques that had formed on his tongue and palate

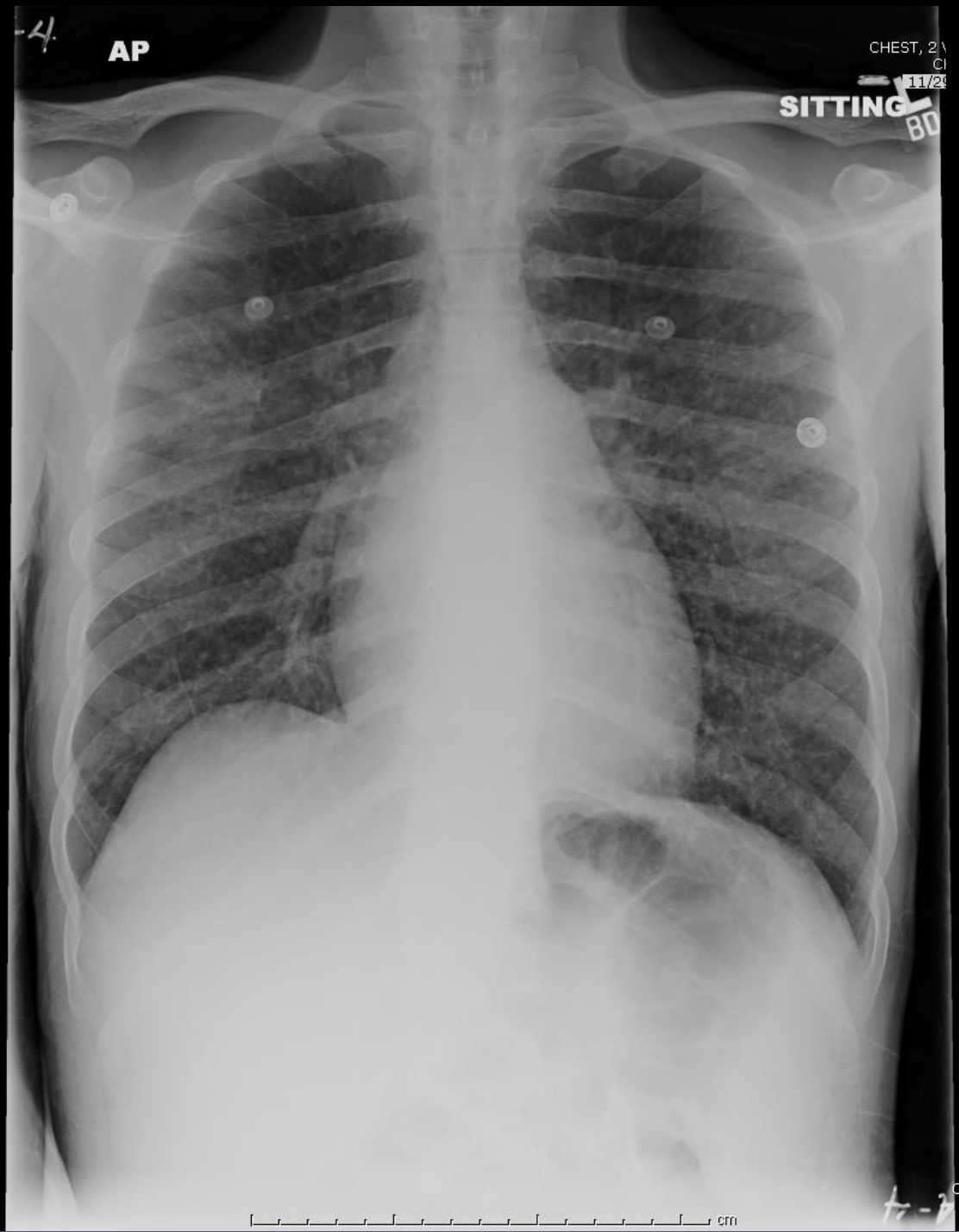
- He had been treated with inhaled steroids at the time and was prescribed Nystatin oral suspension for five days

- One month later the patient returned to the clinic

Follow up

- He complained of having fever, pain on swallowing, weight loss, lack of appetite, dry cough, and shortness of breath. He was sent to the ED from the clinic

- In the emergency department, he had a temperature of 100.5, blood pressure of 98/64, pulse of 108, respiratory rate of 28 and an oxygen saturation of 90% on room air. Chest x-ray was performed and the patient was admitted to the ICU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Differential Diagnosis

- Miliary Tuberculosis
- Disseminated Coccidioidomycosis
- *Pneumocystis* pneumonia (PCP)
- Disseminated Histoplasmosis
- Disseminated Mycobacterium *avium-intracellulare Complex* (MAC)

Hospital Course

- HIV viral load 120,000 copies/mL and CD4 of 28 cells/mm3
- Four drug therapy for Tuberculosis initiated on Day 1 and Fluconazole was administered on Day 3. Liposomal Amphotericin B was administered on Day 4
- The patient expired on Day 5
- Blood cultures became positive for *Coccidioides immitis* on Day 7

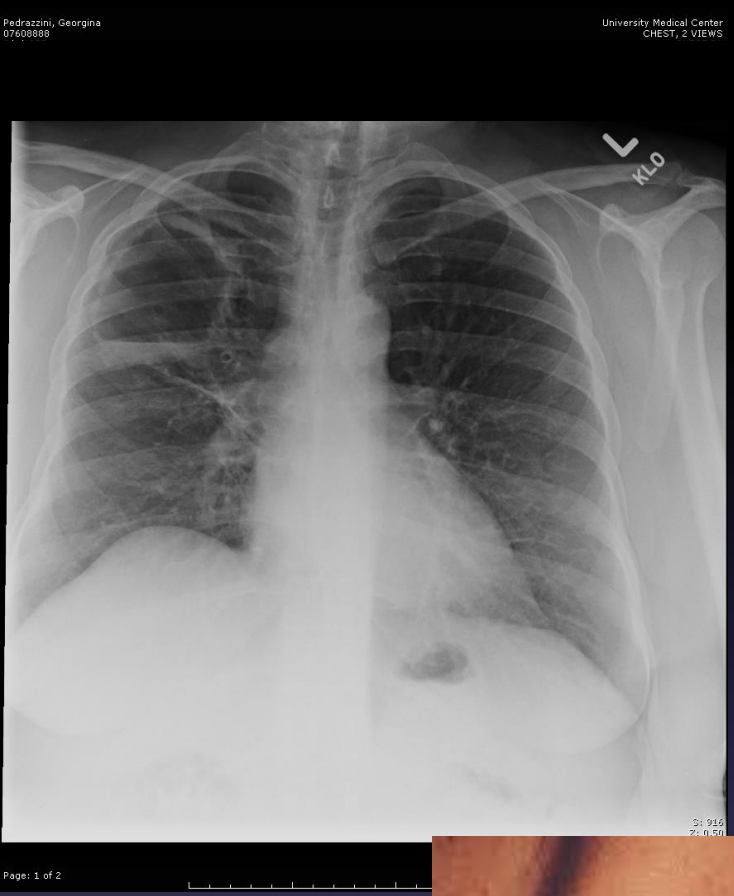
In November 2012, the U.S. Preventive Services Task Force recommended one-time HIV screening for all Americans aged 15 to 64

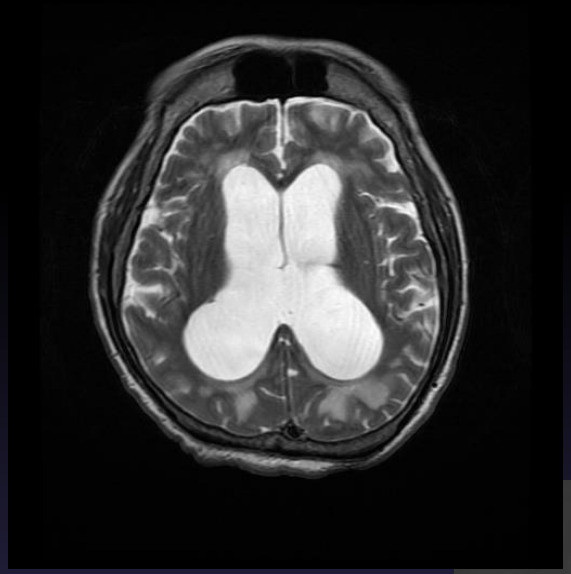
Coccidioidomycosis and HIV/AIDS

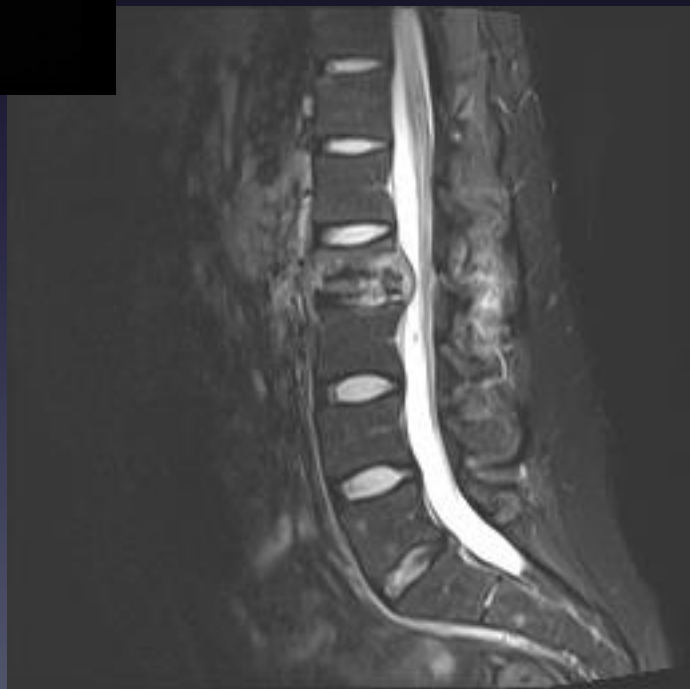
- Risk of developing symptomatic disease is increased in HIV-infected patients living in an endemic area with a CD4 T lymphocyte (CD4) cell counts <250 cells/mm3

- Common syndromes in HIV-infected patients:
  - Focal and Diffuse pneumonia
  - Cutaneous disease
  - Meningitis
  - Bone, liver, or lymph node involvement
  - Positive serology tests without evidence of localized infection

Coccidioidomycosis

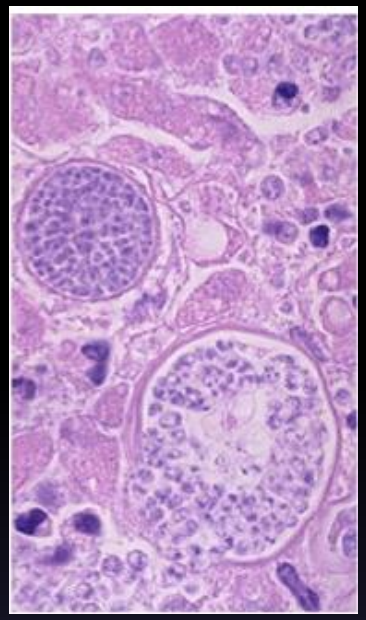






Diagnosis

- Culture or demonstration of spherules on histopathological examination of involved tissue



- Blood cultures are positive in a minority of patients

- Serology: EIA, Immunodiffusion, Tube Precipitin, or Complement Fixation, and Complement Fixation IgG antibody in CSF

- Coccidioidomycosis-specific antigen assay

Fever and Rash

- A 27 year old woman presented to the clinic in December with complaints of fever, rash, sore throat, headache, and myalgia for 5 days

- She denied having ill contacts, recent travel, outdoor activities, or contact with animals

- She worked in an accounting office and reported having a new boyfriend for the past 3 months and denied a history of sexually transmitted diseases

Fever and Rash

- On examination she had a temperature of 38.4^{0} C, Heart Rate of 98, Blood Pressure of 114/68, Respiratory Rate of 16 with an oxygen saturation of 98% on room air

- She was noted to have non-tender cervical lymphadenopathy, pharyngeal edema, and a generalized maculopapular rash involving the thorax, neck, and the face

Diagnostics

- Testing for Influenza, EBV, CMV, Gonorrhea, Syphilis, HIV ELISA, West Nile Virus were all negative

Differential Diagnosis

- Secondary Syphilis
- EBV Mononucleosis
- CMV Mononucleosis
- Acute HIV Infection
- Rocky Mountain Spotted Fever
- West Nile Virus Infection
- Disseminated Gonococcal Infection

Diagnostics

- Testing for Influenza, EBV, CMV, Gonorrhea, Syphilis, HIV ELISA, West Nile Virus were all negative

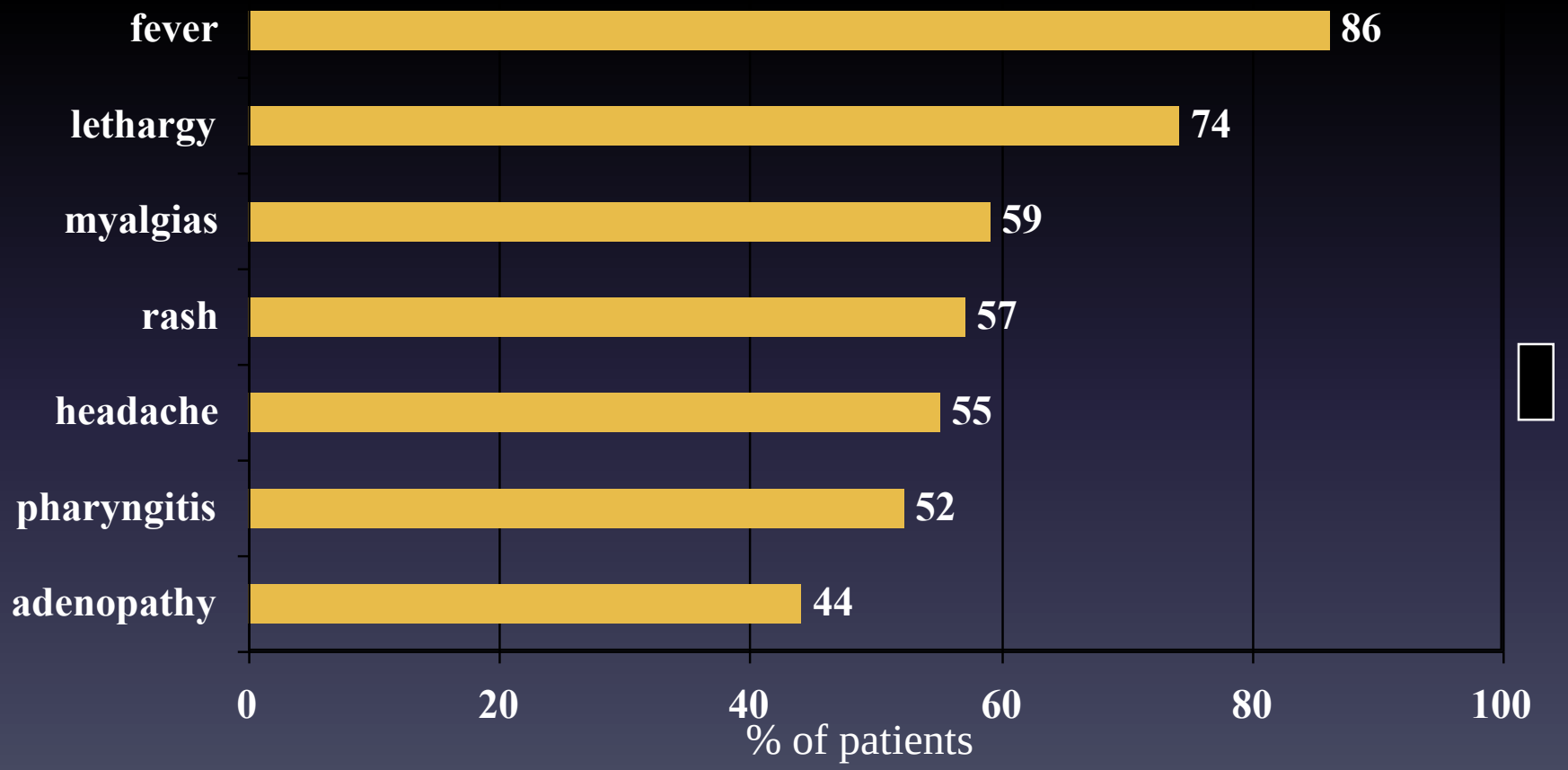
- HIV RNA levels (viral load) >100,000 copies/mL

Primary HIV Infection: Signs and Symptoms

- About 40-90% of patients will be symptomatic
- A mononucleosis-like illness of non-specific signs and symptoms
- Signs and symptoms typically begin 1-4 weeks post-exposure
- High index of suspicion is critical

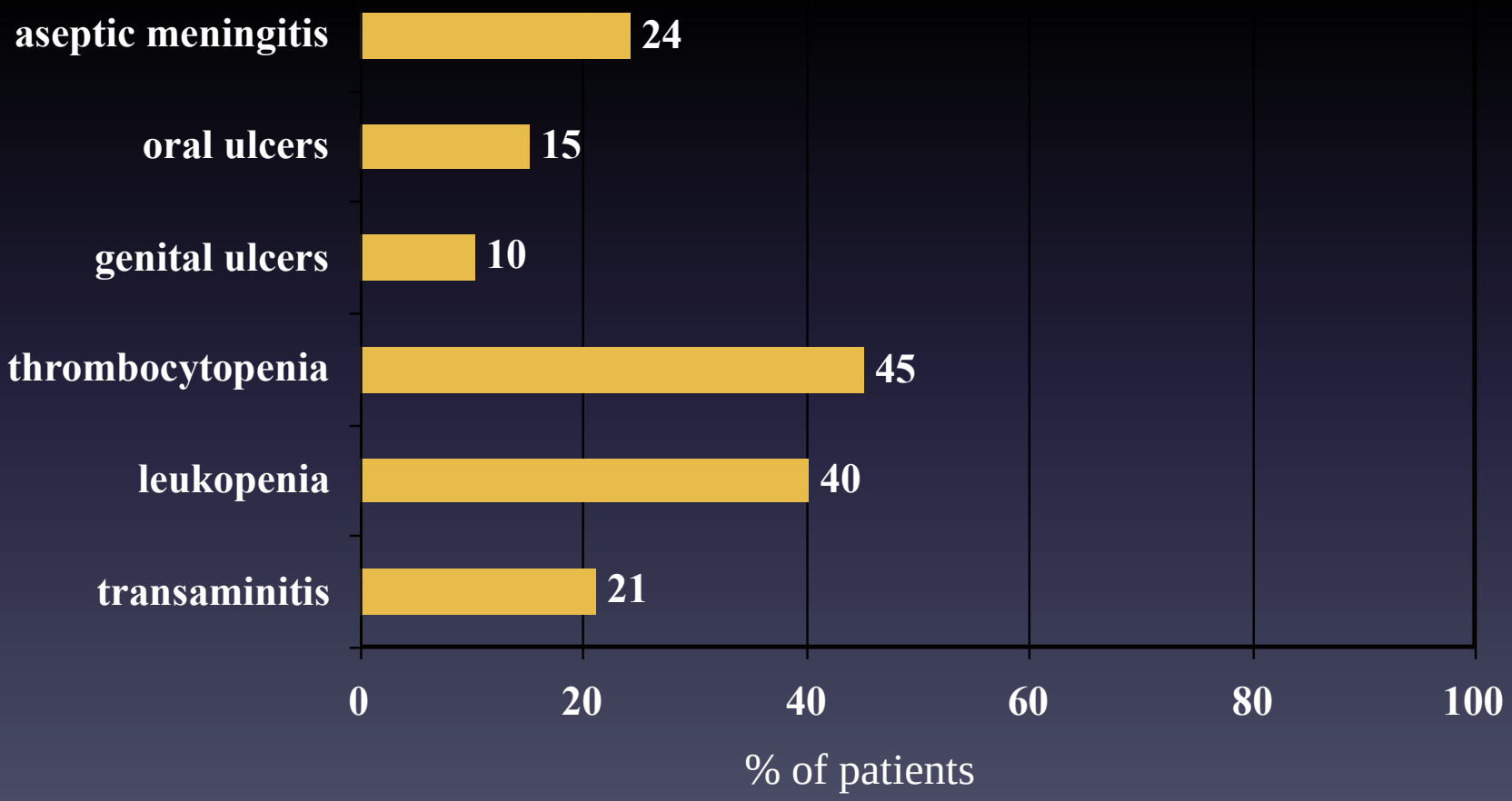
Kahn JO, Walker BD. N Engl J Med. 1998;339:33-39.
Schacker T, et al. Ann Intern Med. 1996;125:257-264.

Primary HIV Infection: Common Signs and Symptoms



Vanhems P et al. AIDS 2000; 14:0375-0381.

Primary HIV Infection: Other Signs and Symptoms



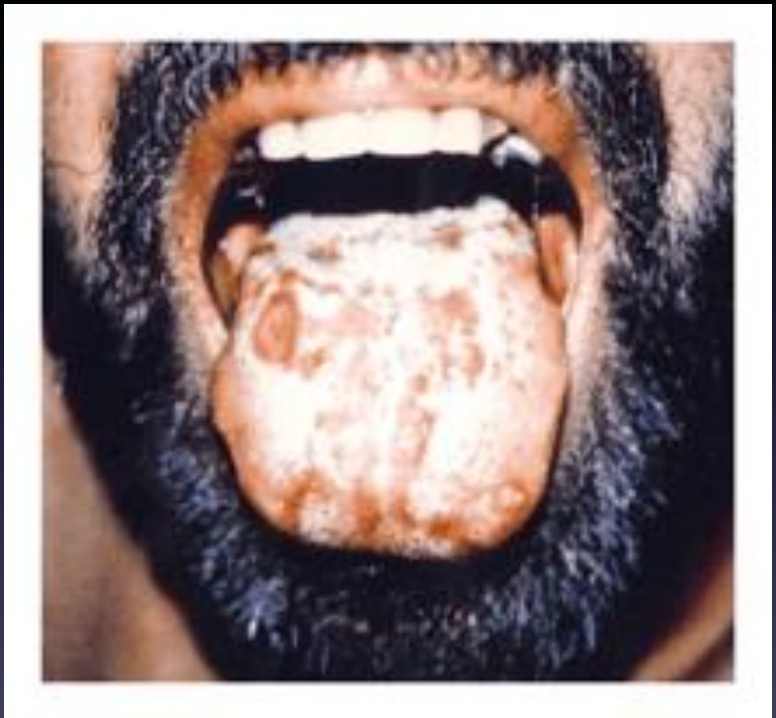
Kahn JO, Walker BD. N Engl J Med. 1998;339:33-39.

Primary HIV Infection

Rash

Trunk and face > limbs
Small pink macules

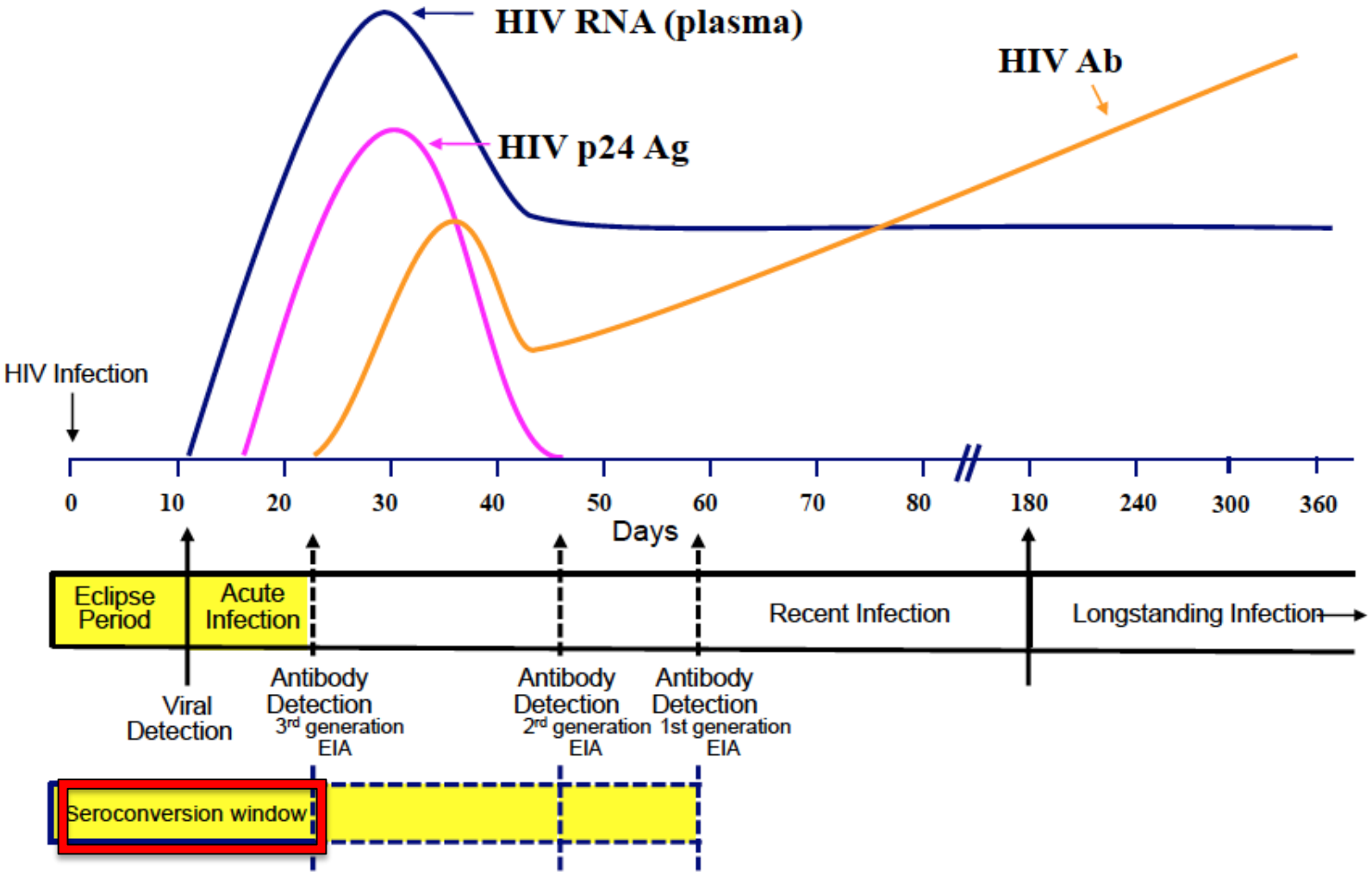
Mucosal Lesions



Oral ulcers, thrush

(Kahn, NEJM, 1998)

What is the Window Period?



Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
  - CD4 count <350 cells/mm^3 **(AI)**
  - CD4 count 350 to 500 cells/mm^3 **(AII)**
  - CD4 count >500 cells/mm^3 **(BIII)**
- Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions:
  - Pregnancy **(AI)** (see perinatal guidelines for more detailed discussion)
  - History of an AIDS-defining illness **(AI)**
  - HIV-associated nephropathy (HIVAN) **(AII)**
  - HIV/hepatitis B virus (HBV) coinfection **(AII)**
- Effective ART also has been shown to prevent transmission of HIV from an infected individual to a sexual partner; therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners (**AI** [heterosexuals] or **AIII** [other transmission risk groups]; see text for discussion).
- Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

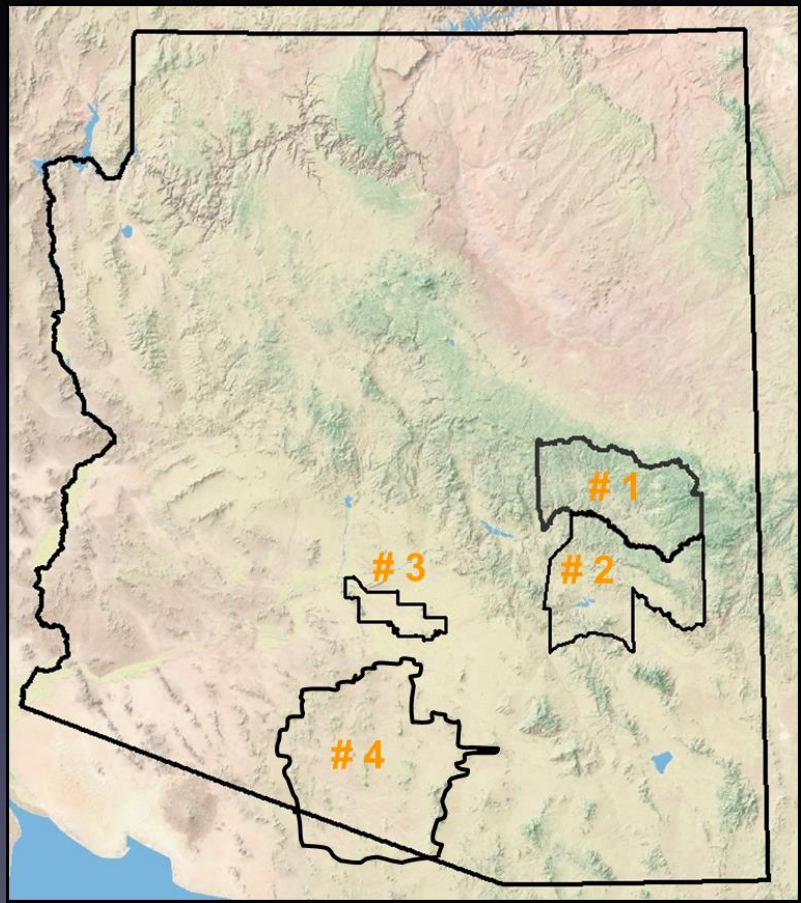
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Fever and Rash

- Secondary Syphilis
- EBV Mononucleosis
- CMV Mononucleosis
- Acute HIV Infection
- Rocky Mountain Spotted Fever
- West Nile Virus Infection
- Disseminated Gonococcal Infection

Rocky Mountain Spotted Fever in Arizona

- From 2002-present, over 266 cases of RMSF have been reported in Arizona
- There have been 21 deaths
  —Case fatality 7%, ~ 15 X higher than the U.S. rate
- Cases occur in clusters due to common household exposures



The Primary Arizona Tick Vector of RMSF

Rhipicephalus sanguineus
Brown dog tick

Arizona Department of Health Services

RMSF: Clinical Manifestations

- Early (first 4 days): Fever, headache, myalgia, abdominal pain + N/V/D; light rash may be present
- Thrombocytopenia, hyponatremia, elevated liver enzymes (AST, ALT) may occur
- Late (day 5 or later): Definitive petechial rash, altered mental status, seizures, cough, dyspnea, arrhythmias, hypotension, and severe abdominal pain

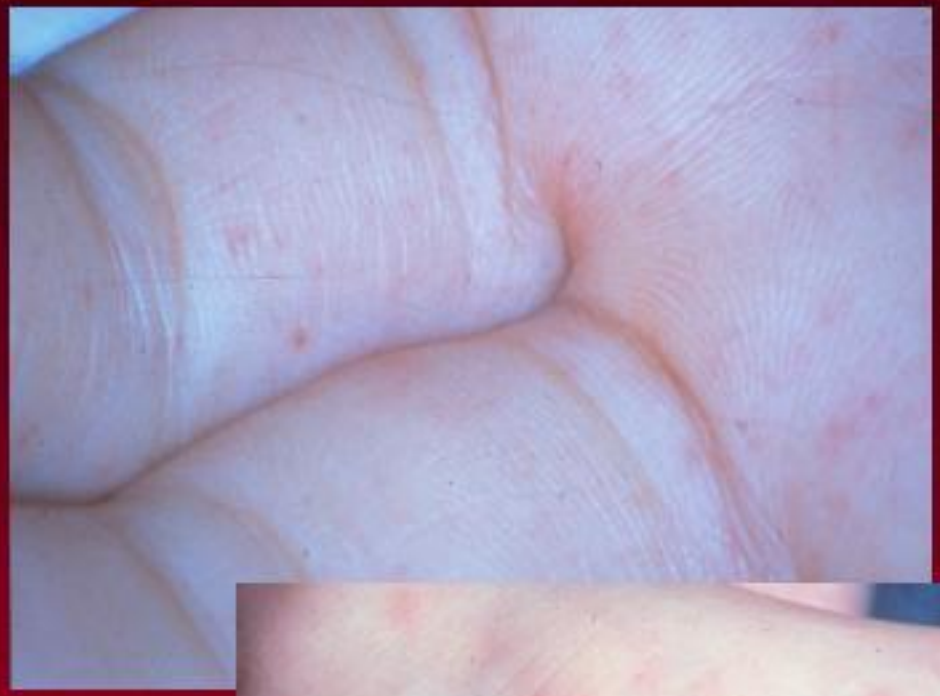
Arizona Department of Health Services

RMSF: The Rash

- Generally not apparent until day 2-5 of symptoms (only seen in 68% of AZ patients)
- Begins as 1 to 5 mm macules progressing to maculopapular
- May begin on ankles, wrists, and forearms, spreads to trunk
- Petechial rash is a late finding, occurs on or after day 6
- Rash may be asymmetric, localized, or absent

Arizona Department of Health Services

Rashes of RMSF



CDC
Centers for Disease Control and Prevention

Antimicrobial Therapy of RMSF

Pregnant adult or tetracycline allergic

→ Chloramphenicol 500 mg qid, less likely to prevent death

Non-pregnant adult or child ≥45 kg

→ Doxycycline 100 mg bid p.o. or i.v.

Child <45 kg

→ Doxycycline 4.4 mg/kg/day in 2 divided doses p.o. or i.v.

Therapy should be continued at least 72 h after defervescence AND until evidence of clinical improvement

Confirmation of *R. rickettsii*

- **Serology (RMSF titer)**
  - Indirect immunofluorescence assay (IFA)
  - Requires paired sera (acute and convalescent)
  - Look for a change (4-fold) in antibody titers for confirmed infections
  - Positive single titers or titers that do not rise are considered probable cases

- **PCR**
  - Available at CDC. Can give a rapid result (48 hours)
  - Skin biopsy (2-4mm)
  - Whole blood of severely ill/fatal cases
  - ***NOTE: Negative PCR does not rule-out RMSF***

“Swollen Foot”

- A 65-y/o Woman presented to the clinic because of pain and swelling involving the dorsum of her right foot which she thought was due to an insect bite

- She was prescribed TMP/SMX for possible MRSA infection

- The next day, her foot became swollen, painful, and she felt ill and was febrile. At 5 pm her daughter found her obtunded

“Swollen Foot”

- In the ED she appeared acutely ill and confused. She was found to be hypotensive and tachycardic as well
- The skin of her lower extremity appeared cyanotic and was cool
- The entire foot was mottled and swollen, with a black eschar on the dorsum; the swelling extended up the knee

Differential Diagnosis

- Erysipelas
- Diabetic Muscle Infarction
- Necrotizing fasciitis
- Myonecrosis (Gas Gangrene)
- Vibrio vulnificus associated myositis

Necrotizing Fasciitis

- Type I necrotizing fasciitis, at least one anaerobic species is isolated in combination with one or more facultative anaerobic species such as streptococci (other than group A) and members of the Enterobacteriaceae

- Type II, group A streptococci are isolated alone or in combination with other species, most commonly *S. aureus*

Clinical Presentation

Clinical features suggestive of necrotizing fasciitis:

- Severe, constant pain
- Bullae (occlusion of deep blood vessels that traverse the fascia)
- Skin necrosis or ecchymosis that precedes skin necrosis
- Gas in the soft tissues, detected by palpation or imaging
- Edema that extends beyond the margin of erythema
- Cutaneous anesthesia
- Systemic toxicity (fever, leukocytosis, delirium, and renal failure)
- Rapid spread, especially during antibiotic therapy

Diagnosis

- Prompt diagnosis is of paramount importance because of the rapidity with which the process can progress and a mortality rate of 24% to 34%

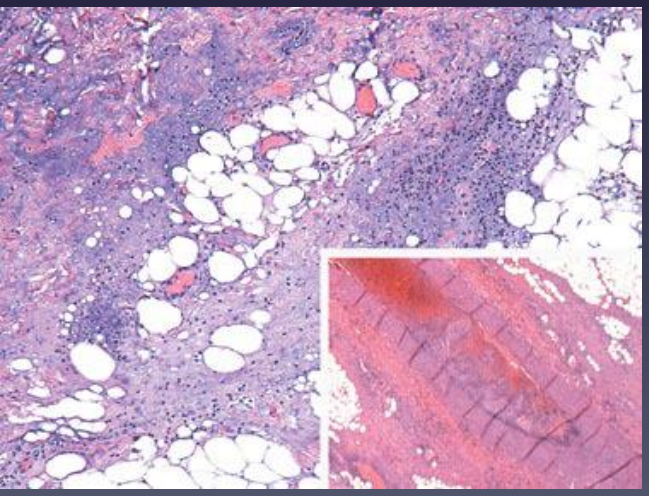
- CT scanning and magnetic resonance imaging (MRI) can demonstrate subcutaneous and fascial edema, as well as tissue gas

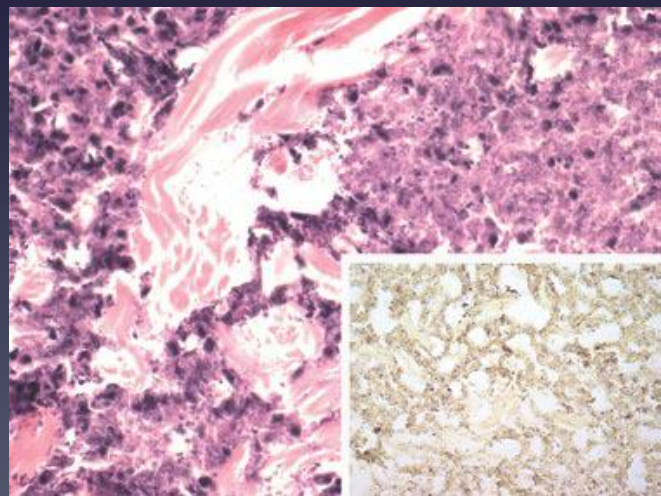
- The most expeditious route to diagnosis is through surgical exploration or biopsy, without introducing delay for imaging studies

Diagnosis

- Frozen section examination of biopsy specimens is helpful for early diagnosis

- Pathologic features include tissue destruction, thrombosis of blood vessels, abundant bacteria spreading along fascial planes, and infiltration of acute inflammatory cells





Treatment

- Immediate surgical debridement is essential

- Necrotic fat and fascia should be excised. A second-look procedure is frequently necessary 24 hours later to ensure adequacy of the initial debridement

- Treatment should be tailored to Gram stain, culture, and sensitivity results when available. Empiric treatment consist of broad-spectrum antimicrobials active against gram-positive, gram-negative, and anaerobic organisms

“Terrible Headache”

- A healthy 37 year old man presented to the clinic with complaints of sinus pain and headaches of two weeks duration. He was treated empirically with amoxicillin/clavulanate but his symptoms did not resolve

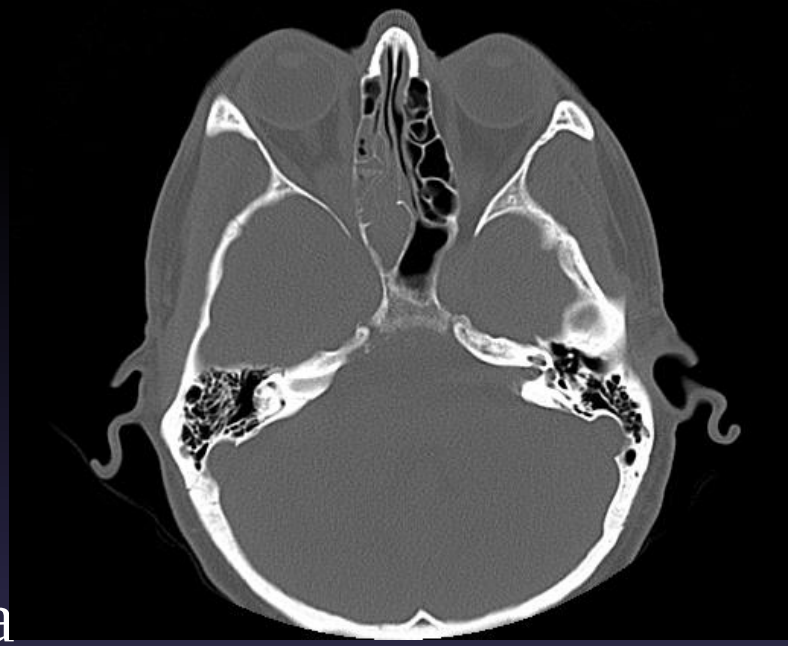
- He returned to the clinic one month later with reoccurrence of symptoms. Cultures obtained by his ENT revealed growth of *Pseudomonas aeruginosa*. He was treated with ciprofloxacin but without improvement of his symptoms

Differential Diagnosis

- Invasive Fungal Sinusitis
- Orbital Cellulitis
- Complicated Bacterial Sinusitis
- Zoster sine herpete

“Terrible Headache”

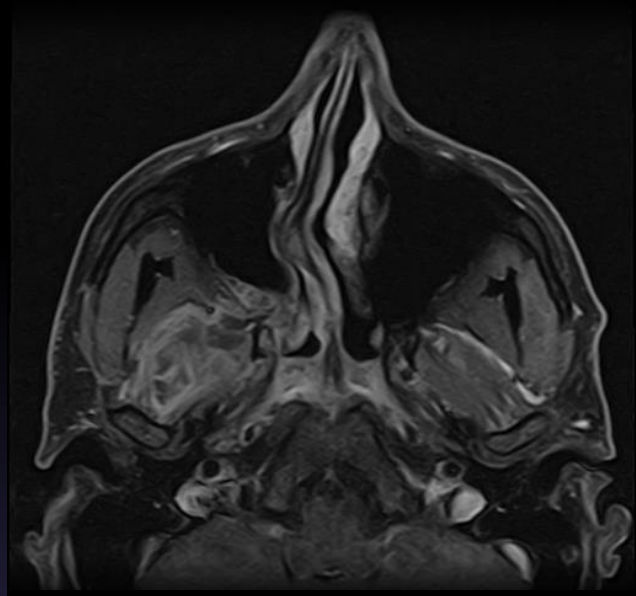
- He returned with complaints of worsening headache, photophobia, diplopia, and loss of right lateral movement of the right eye

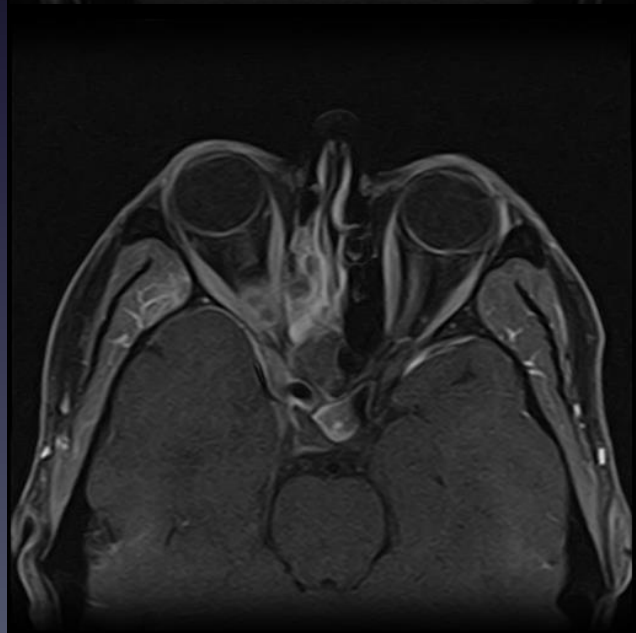


- On imaging he was found to have a right infratermporal mass extending to the right sinus cavity

“Terrible Headache”

- MRI: Infiltrative mass involving the right infratemporal and pterygopalatine fossa, ethmoid and maxillary sinuses, extension into the right orbit
- He underwent emergent endoscopic evaluation and ethmoidectomy
- Findings included the presence of necrotic tissue with impacted mucopurulernt debris



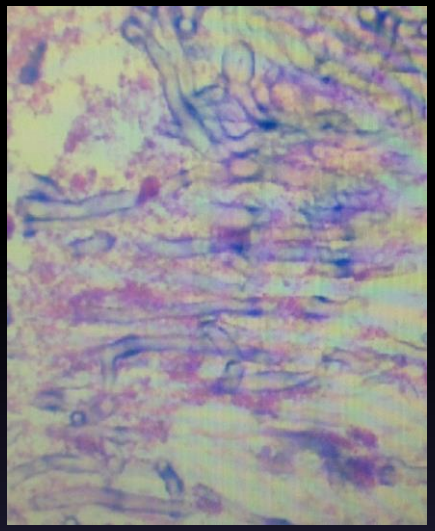


“Terrible Headache”

- Histopathology and microbiology confirmed infection with *Aspergillus fumigatus*

- Initial therapy included liposomal Amphotericin B and Voriconazole

- He underwent several operations and was evaluated for an underlying immunodeficiency state



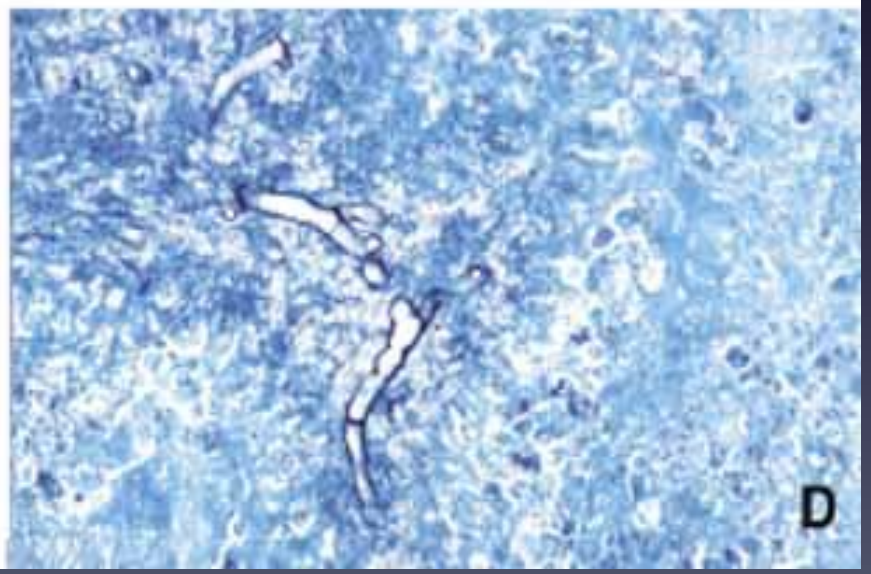
Invasive Fungal Sinusitis

- The fungi most commonly found in human infections are *Aspergillus*, *Fusarium*, the Mucorales, and dematiaceous (brown-black) molds

- These organisms are ubiquitous in nature

- Mucormycosis in severely immunosuppressed patients is often fatal, with the mortality rate ranging from 68 to 100%

Mucormycosis

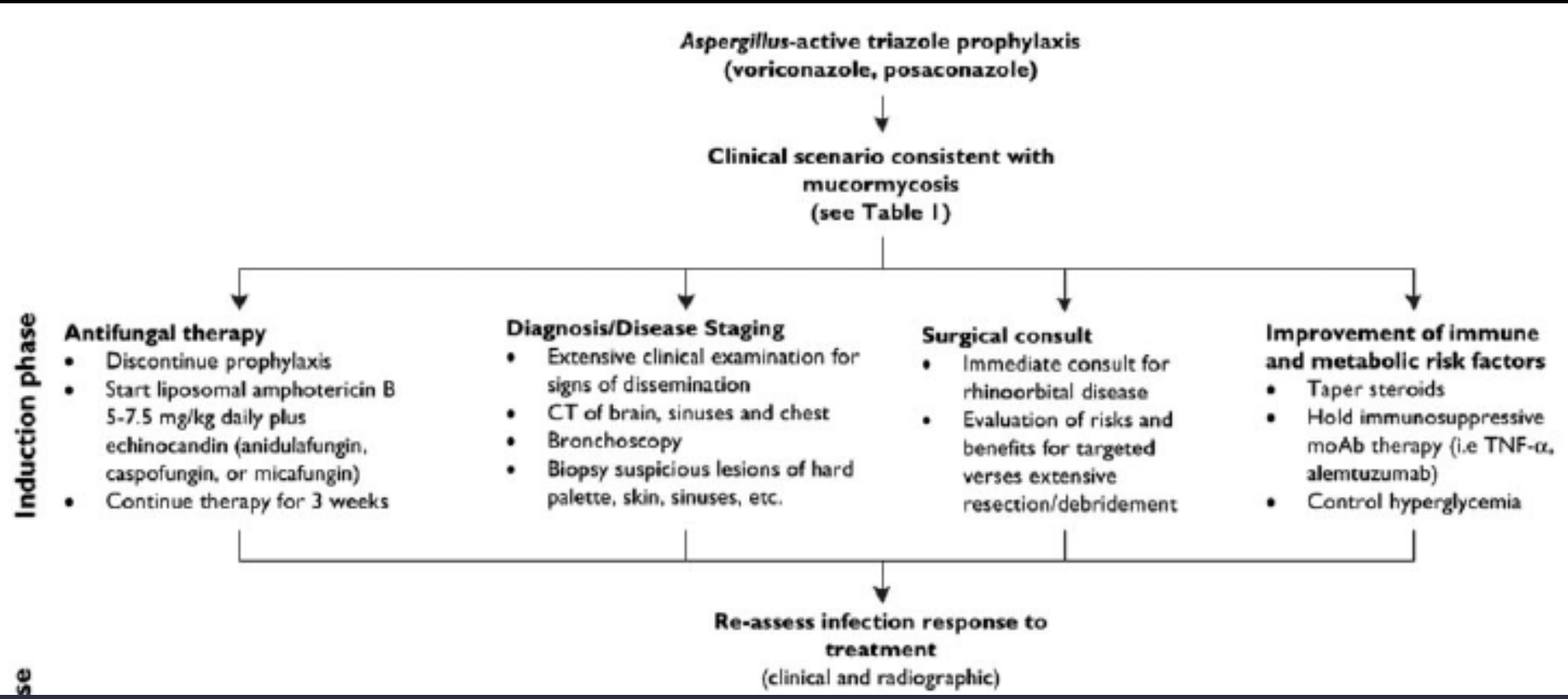


Risk Factors

Table 2 Factors predisposing patients to zygomycosis

Diabetes mellitus
Diabetic ketoacidosis
Poorly controlled diabetes mellitus
Chronic metabolic acidosis
Renal failure
Chronic salicylate poisoning
Deferoxamine therapy
Iron overload
Immunosuppression
Neutropenia (due to malignancies or chemotherapy)
Corticosteroid therapy
Organ or hematopoietic cell transplantation
HIV infection
Skin or soft tissue breakdown
Burn
Trauma
Surgical wound
Miscellaneous
Intravenous illicit drug use
Neonatal prematurity
Malnourishment
Prolonged use of broad-spectrum antimocrobial agents

Management


Induction phase
Aspergillus-active triazole prophylaxis (voriconazole, posaconazole)
Clinical scenario consistent with mucormycosis (see Table 1)
Antifungal therapy
• Discontinue prophylaxis
• Start liposomal amphotericin B 5-7.5 mg/kg daily plus echinocandin (anidulafungin, caspofungin, or micafungin)
• Continue therapy for 3 weeks
Diagnosis/Disease Staging
• Extensive clinical examination for signs of dissemination
• CT of brain, sinuses and chest
• Bronchoscopy
• Biopsy suspicious lesions of hard palette, skin, sinuses, etc.
Surgical consult
• Immediate consult for rhinoorbital disease
• Evaluation of risks and benefits for targeted verses extensive resection/debridement
Improvement of immune and metabolic risk factors
• Taper steroids
• Hold immunosuppressive moAb therapy (i.e TNF-α, alemtuzumab)
• Control hyperglycemia
Re-assess infection response to treatment
(clinical and radiographic)

Red Herrings

Initial Diagnosis: UTI

- A 75 year old man was seen in the clinic for having had fever, fatigue, and weight loss. He was admitted for further workup

- Urinalysis indicated hematuria and pyuria and cultures grew >100,000 CFU/mL of *E. Coli*

- One out of 4 blood cultures grew Viridans streptococci which was regarded as a contaminant

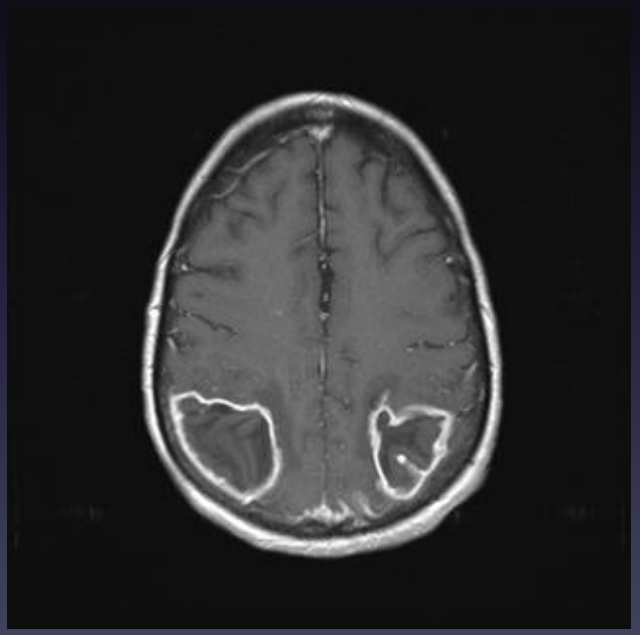
Initial Diagnosis: UTI

- He was discharged with a seven day course of Ciprofloxacin, but his symptoms persisted for another two months and he was prescribed several courses of antibiotics for reoccurring UTIs

- He presented to the ED three months after the initial hospitalization with altered mental status and heart failure

- He complained of back pain described as stabbing in nature, lower extremity weakness with decreased sensation, difficulty walking, and bladder dysfunction

Actual Diagnosis: Subacute Bacterial Endocarditis due to Viridans streptococci resulting in spinal epidural and brain abscesses



Initial Diagnosis: Complicated UTI

- An 82 year old man presented to the clinic accompanied by his son who reported that his father was having fever, fatigue, urinary incontinence, lack of appetite, confusion, and was walking naked in the house

- Urinalysis was performed which showed significant bacteruria and pyuria

- He was diagnosed with a UTI and was prescribed Levofloxacin for 7 days

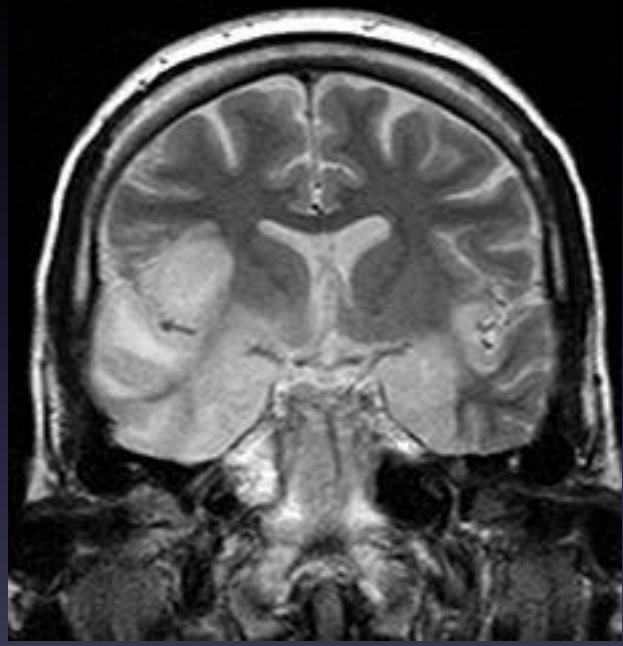
Initial Diagnosis: Complicated UTI

- The following day he continued to have fever and worsening confusion

- He was transferred to the ED that evening with reports of having developed aphasia, ataxia, and an episode of seizure

HSV Encephalitis

- Pathogenesis: Reactivation of virus in cranial nerve ganglia and retrograde spread along axons
- Focal involvement of temporal lobe
- Personality changes, obtundation, seizures, focal neurologic findings
- Intravenous Acyclovir is recommended for the treatment of Herpes Encephalitis



Initial Diagnosis: Uncomplicated UTI

- A 65 y/o woman with poorly controlled diabetes, SLE on immunosuppressive therapy, nephrolithiasis, and frequent episodes of cystitis presented to the clinic with c/o dysuria, fever, abdominal pain, and flank pain

- Urinalysis revealed significant bacteruria and pyuria and urine culture later grew $>10^5$ CFU/mL of Enterobacter species

- She was prescribed TMP/SMX for 14 days and asked to follow up if her symptoms did not improve

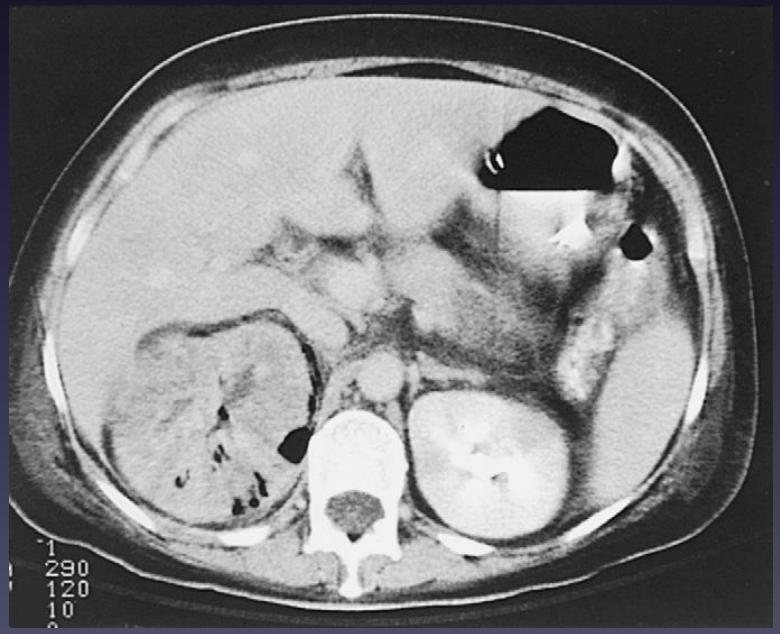
Initial Diagnosis: Uncomplicated UTI

- 48 hours later her symptoms worsened with continued fever, rigors, dysuria, abdominal pain, and altered mental status

- She was transferred to the ED and found to meet criteria for sepsis

Actual Diagnosis: Emphysematous Pyelonephritis

CT of the abdomen revealed extension of abscess with gas into the right pararenal space



Actual Diagnosis: Emphysematous Pyelonephritis

- The patient was started on broad spectrum antibiotics, supportive therapy, and underwent nephrectomy

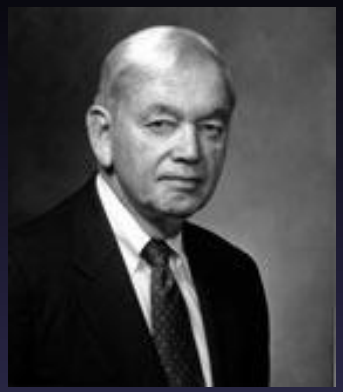
- Blood cultures on day three grew Enterobacter species

FEVER OF UNEXPLAINED ORIGIN: REPORT ON 100 CASES

ROBERT G. PETERSDORF* AND PAUL B. BEESON

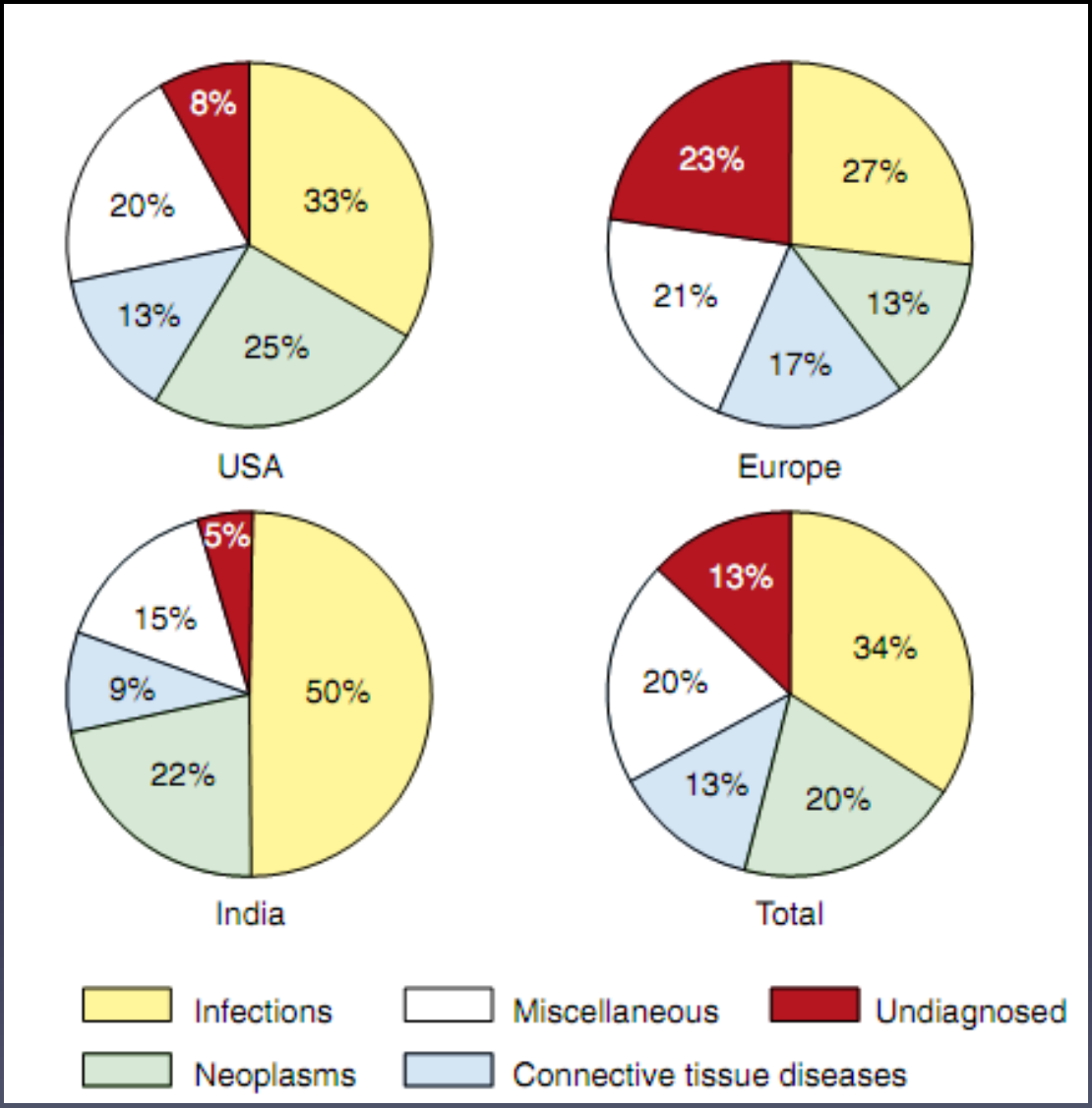
From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

Medicine (Baltimore) February, 1961



Fever of unknown origin (FUO): (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 one week of inpatient investigation

Etiology and Classification



- Classic
- Nosocomial
- Neutropenia/Transplant
- HIV/AIDS

Infectious Etiology

- Intra-abdominal abscess, Endocarditis, Bone and Joint infections
- Viral (EBV, CMV, HIV, Dengue,…)
- Bacterial (Tuberculosis, typhoid, brucellosis, Q Fever, syphilis, rickettsia,…)
- Fungal (Endemic mycosis,…)
- Parasitic (Malaria, hepatic amebiasis,…)
- Indirect (Hemophagocytic lymphohistiocytosis)


SATURDAY NIGHT FEVER


spring fever
BRECKENRIDGE


CABIN FEVER


Simpson Fever
Catch the Fever...


TEPPANYAKI GRILL
SUSHI FEVER
SUSHI FEVER

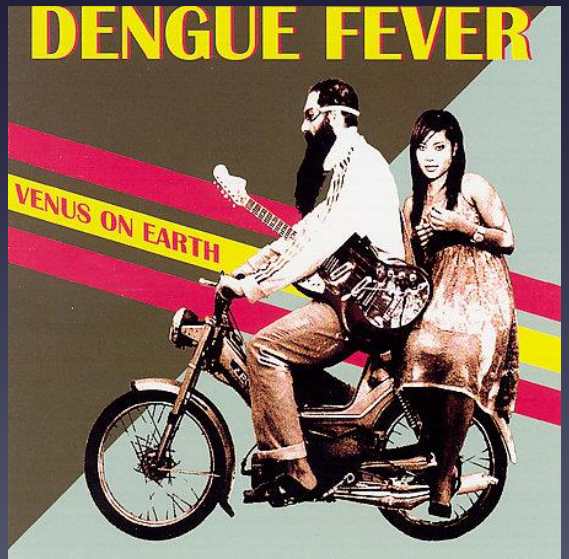

DENGUE FEVER
VENUS ON EARTH

TABLE 51-7 General Diagnostic Evaluation of Patients with Fever of Unknown Origin

- Comprehensive history
- Repeated physical examinations
- Complete blood count
- Routine blood chemistry determinations
- Urinalysis, including microscopic examination
- Chest radiograph
- Erythrocyte sedimentation rate
- Antinuclear antibodies
- Rheumatoid factor
- Blood cultures: three or more separate specimens obtained in absence of antimicrobial therapy
- Cytomegalovirus IgM antibodies or viral detection in blood
- Heterophile antibody test in children and young adults
- Tuberculin skin test
- Computed tomography of abdomen, pelvis, or other sites
- Magnetic resonance imaging
- Radionuclide scans
- Human immunodeficiency virus antibodies or viral detection assay
- Further evaluation of any abnormality detected by above tests
- Venous duplex imaging of lower limbs

Adapted from Arrow PM, Flaherty JP. Fever of unknown origin. *Lancet.* 1997;350:575-580, with permission from Elsevier.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"I'm not sure what's wrong with you. We'll have to wait for the results to come back from the autopsy."