Fever of Unknown Origin

INFECTION DISEASES
Stephanie W. Smith

DIFFERENTIAL DIAGNOSIS
This list is not exclusive, but highlights some important causes of FUO after the common causes of fever have been excluded:

**INFECTIONS**—TB (pulmonary, extrapulmonary, miliary), abscess (liver, splenic, perinephric, psoas, diverticular, pelvis), osteomyelitis, endocarditis, prosthetic associated infections

**NEOPLASTIC**—hematologic (lymphoma, leukemia, multiple myeloma, myelodysplastic syndrome), solid tumors (renal cell, hepatoma)

**COLLAGEN-VASCULAR**—vasculitis (giant cell arteritis, Still’s disease, polyarteritis nodosa, Takayasu’s arteritis, granulomatosis with polyangiitis, mixed cryoglobulinemia), lupus, rheumatoid arthritis

**DRUGS**—antimicrobials (sulfonamides, penicillins, nitrofurantoin, antimalarials), antihistamines, antiepileptics (barbiturate, phenytoin), NSAIDs/ASA, antihypertensives (hydralazine, methyldopa), antiarrhythmics (quinidine, procainamide), antithyroid, iodides, quinine, illicit (cocaine)

**UNCOMMON CAUSES OF FUO**—central fever, endocrine (hypothalamic dysfunction, hyperthyroidism, pheochromocytoma, adrenal insufficiency), infections (dental abscess, Q fever, leptospirosis, psittacosis, tularemia, melioidosis, syphilis, gonococemia, chronic meningococemia, Whipple’s disease, yersiniosis, brucellosis), hereditary periodic fever syndromes (familial Mediterranean fever, PFAPA syndrome [Periodic Fever with Aphthous Stomatitis and Adenitis], TNFR-1-associated periodic syndrome, hyper-IgD syndrome, Muckle–Wells syndrome, familial cold autoinflammatory syndrome), alcoholic hepatitis, hematoma, factitious fever

PATHOPHYSIOLOGY

**DEFINITIONS**

- **FUO**—≥ 38.3 °C ([≥101 °F], duration ≥3 weeks, diagnosis uncertain after 3 days in hospital or three outpatient visits)
- **NOSOCOMIAL FUO**—hospitalized patients, ≥38.3 °C ([≥101 °F]), diagnosis uncertain after 3 days and infection not present or incubating on admission
- **IMMUNE-DEFICIENT (NEUTROPENIC) FUO**—> 38.3 °C ([≥101 °F]), >3 days, neutrophil count ≤500/mm³. See p. 260 for details
- **HIV-RELATED FUO**—HIV patients, ≥38.3 °C ([≥101 °F], duration ≥3 weeks for outpatients or ≥3 days for inpatients
- **FEVER, NYD**—persistent fever that has not yet met the definition for FUO

**HISTORY**—pattern and duration of fever, associated symptoms (cough, dyspnea, hemoptysis, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, hematuria, neck stiffness, headache), rash (palpable purpura, exanthem), exposure (food, water, plants, animals, insects, infected human secretions), weight loss, night sweats, travel history, sexual history, HIV risk factors, immunizations, past medical history (rheumatologic disorders, malignancy, alcohol), medications

**PHYSICAL**—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), temporal artery, abdominal examination (hepatosplenomegaly), prostate examination, skin lesions (morphology, distribution), tick bite marks, joint examination
DIAGNOSIS AND PROGNOSTIC ISSUES

DIAGNOSIS — the most important diagnostic strategy is a careful history and physical examination with frequent reassessment.

PROGNOSIS — up to 30–50% will not have a diagnosis despite detailed workup; 5-year mortality in those without a diagnosis is 3%.

MANAGEMENT

EMPIRIC ANTIBIOTICS — ONLY if suspect infectious etiology and therapy cannot be delayed due to severity of patient’s disease (see EMPIRIC ANTIBIOTICS p. 289). In general, therapeutic trials of antimicrobials or steroids are discouraged.

TREAT UNDERLYING CAUSE

INVESTIGATIONS

BASIC

- LABS — CBC, LDH, Cr, AST, ALT, ALP, bilirubin, ESR, CRP, ANA, RF, C3, C4, ANCA, cryoglobulin

- MICROBIOLOGY — blood C&S (Mycobacteria, sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, serology [HBV, HCV, HIV, monosanpop, CMV IgM, endemic fungi])

- IMAGING — CXR, echocardiogram (if suspect endocarditis, CT chest/abd/pelvis as guided by symptoms, FDG-PET [may be useful for identifying sites of inflammation and malignancy in FUO])

SPECIAL

- ECG
- TUBERCULIN SKIN TEST
- BIOPSY — affected tissue (e.g. bone marrow biopsy)

DIFFERENTIAL DIAGNOSIS

INFECTIONS

- GRAM-POSITIVE COCCI — scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, acute rheumatic fever (erythema marginatum, subcutaneous nodules)

- GRAM-NEGATIVE COCCI — meningococccemia (purpura), disseminated gonococcal infection

- GRAM-NEGATIVE BACILLI — Salmonella typhi, Pseudomonas (erythema gangrenosum), Vibrio vulnificus

- ENDOCARDITIS

- SPIROCHETES — Borrelia burgdorferi (Lyme erythema migrans), Treponema pallidum (chancre, secondary syphilis)

- RICKETTSIAL — Rocky Mountain spotted fever, ehrlichiosis, typhus

- VIRAL EXANTHEM — acute HIV, mononucleosis, rubella, measles, roseola, erythema infectiosum, chickenpox, shingles, coxsackie virus, echovirus

- FUNGAL — Blastomyces, Coccidioides, Histoplasma

RHEUMATOLOGIC

- SEROPOSITIVE — lupus, dermatomyositis

- SERONEGATIVE — inflammatory bowel disease, reactive arthritis

DIFFERENTIAL DIAGNOSIS (CONT’D)

- VASCULITIS — granulomatosis with polyangiitis, polyarteritis nodosa

- BEHÇET’S DISEASE

MALIGNANCY — lymphoma, leukemia, metastatic, paraneoplastic

MEDICATIONS — penicillins, cephalosporins, sulfas, barbiturates, phenytoin, procainamide, quinidine

OTHERS — sarcoidosis, erythema nodosum; Sweet’s syndrome (acute febrile neutrophilic dermatosis)

CLINICAL FEATURES

SETTINGS

- AGE — viral exanthems, scarlet fever, and acute rheumatic fever are more likely in children. Mononucleosis is more common in young adults

- SEASON — tick-borne diseases are more common in spring and summer. Coxsackie virus and echovirus are more common in summer and fall. Meningococcus and parvovirus are more common in winter and spring

- GEOGRAPHIC LOCATION — Lyme disease in Pacific northwest, the Midwest, and the northeast USA and some southern Canadian locations. RMSF in south-central and Atlantic
CLINICAL FEATURES (CONT’D)

states. Ehrlichiosis in midwestern, south-central, and southeastern states. Tularemia in western, southeastern, and south-central states and Canada. Endemic fungal infections include Blastomyces dermatitidis (southeastern states, Manitoba, and Ontario), Coccidioides immitis (southwestern states), and Histoplasma capsulatum (Mississippi, Ohio River valleys, and Quebec)

HISTORY—pattern and duration of fever, associated symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache), rash (prodrome, location, progression, treatment), exposure (food, water, plants, animals, infected human secretions), weight loss, night sweats, travel history, sexual history, immunizations, past medical history (rheumatologic disorders, malignancy), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution), tick bite eschar, joint examination

INVESTIGATIONS

BASIC
• LABS—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, ESR, urinalysis
• MICROBIOLOGY—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, monospot test, CMV IgM, EBV, HIV, and other serologies (e.g. rickestsial serology)

SPECIAL
• LUMBAR PUNCTURE—if suspect meningococcus
• SKIN BIOPSY—dermatology consult
• INFLAMMATORY WORKUP—CRP, ANA, ENA

MANAGEMENT

ISOLATION PRECAUTIONS—droplet/airborne plus contact precautions for uncertain diagnosis; for purpura with bacterial sepsis, institute droplet and contact isolation precautions. See p. 304 for more details

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

RICKETTSIAL INFECTIONS (WITHIN NORTH AMERICA)

• THEMES—all transmitted by ticks, except Q fever (Coxiella burnetii). All associated with a rash, myalgias, and headache, except Q fever and ehrlichiosis. All involve some degree of vasculitis and DIC as part of pathogenesis. All can be treated with doxycycline
• ROCKY MOUNTAIN SPOTTED FEVER—Rickettsia rickettsii transmitted by ticks. Most common in mid-Atlantic states. Macular/maculopapular rash begins on extremities and moves centrally, involves palms/soles. Treat with doxycycline
• MURINE TYPHUS—flea vector. Rash begins centrally and moves peripherally. Treat with doxycycline or chloramphenicol
• EHRlichia—E. chaffeensis (human monocytic ehrlichiosis) transmitted by lone star tick. Peaks in May to July. Infects lymphocytes, monocytes, and neutrophils intracellularly. Fever, headache, myalgia, leukopenia, thrombocytopenia, and elevated transaminases; maculopapular or petechial rash in 1/3. Human granulocytic anaplasmosis is caused by a related Ehrlichia and produces similar illness without rash. Transmitted by Ixodes tick and co-infection with Lyme disease possible. Treat with doxycycline
• Q FEVER—Coxiella burnetii transmitted by respiratory spread from infected animal body fluids (e.g. cattle, sheep, goats, cats). No rash. Fever, pneumonitis, hepatitis, endocarditis, CNS symptoms. Treat with doxycycline

LYME DISEASE

• PATHOPHYSIOLOGY—Borrelia burgdorferi transmitted by tick bite after attachment for >24 h; think about concomitant tick borne diseases
• CLINICAL FEATURES—most common tick-borne disease in USA, particularly coastal Atlantic States and California during spring and summer
• STAGE 1 (EARLY)—first 3–30 days, erythema migrans, fever, meningismus, lymphadenopathy
• STAGE 2 (DISSEMINATED)—weeks to months, hematogenous spread with neurological symptoms (facial nerve palsy, lymphocytic meningitis, encephalitis, chorea, myelitis, radiculitis, peripheral neuropathy) and carditis (AV block, dilated cardiomyopathy); may have multiple skin lesions of erythema migrans
SPECIFIC ENTITIES (CONT’D)

- **STAGE 3 (LATE)**—months to years, mono- or oligoarthritis, acrodermatitis chronica atrophicans (in Europe), progressive encephalitis, dementia. Not amenable to antibiotic therapy
- **DIAGNOSIS**—seology (anti-B. burgdorferi ELISA). If positive, confirm with Western blot
- **PREVENTION**—protective clothing and tick repellants. After tick bite (>36 h in hyperendemic area), consider **doxycycline** 200 mg × 1 dose within 72 h of the tick bite
- **TREATMENTS**—stage 1 (**doxycycline** 100 mg PO BID × 10–21 days, or **cefuroxime** 500 mg PO BID × 10–21 days). **Lyme carditis** (**ceftriaxone** 2 g IV × 14–21 days if third degree AV block; otherwise, same as stage I with oral antibiotics). **Neurologic Lyme** (**ceftriaxone** 2 g IV × 14–21 days). **Lyme arthritis** (**doxycycline** 100 mg BID × 28 days, amoxicillin)

- **JARISCH–HERXHEIMER REACTION**—up to 15% of patients may experience transient worsening of symptoms during first 24 h of treatment. This results from the host immune response to antigen release from dying organisms (typically Lyme and syphilis) causing fever, chills, myalgias, and exacerbation of rash

**BABESIOSIS** (malaria like; does not cause rash)

- **PATHOPHYSIOLOGY**—B. microti (USA) or B. divergens (Europe) transmitted by Ixodes ticks (which also transmit Lyme disease and Ehrlichia) → fever, chills, sweats, malaise, myalgias, arthralgias, headache 5–33 days after, particularly in immunosuppressed individuals

- **CLINICAL FEATURES**—endemic in southern New England, southern New York, Wisconsin, and Minnesota

- **DIAGNOSIS**—blood smear (‘Maltese cross’ formations, not seen in malaria), PCR, serology

- **TREATMENTS**—atovaquone plus azithromycin

**RATIONAL CLINICAL EXAMINATION SERIES:**
**DOES THIS PATIENT HAVE ERYTHEMA MIGRANS?**

| Sens (%) |
|----------|
| History (US studies)                    |
| Systemic symptoms                      | 65 |
| Fatigue                                 | 47 |
| Headache                                | 36 |
| Myalgias                                | 35 |
| Arthralgias                             | 35 |
| Fever                                   | 33 |
| Pruritus                                | 33 |
| Stiff neck                              | 31 |
| History of a tick bite                  | 26 |
| Dysesthesia                             | 20 |
| Nausea and vomiting                     | 11 |

**Physical (US studies)**

- **Solitary lesion**                     | 81 |
- **Lymphadenopathy**                     | 22 |
- **Multiple lesions**                    | 21 |
- **Central clearing of rash**            | 19 |

**APPROACH**—“no single component of the history or physical examination emerges as one that makes the diagnosis of erythema migrans highly likely. These signs and symptoms have not been examined in combination. Laboratory testing has limited utility. In endemic areas, the combination of history of a tick bite, a solitary lesion of appropriate size, morphology and presence of systemic symptoms is consistent with erythema migrans. In non-endemic areas, these same factors are also suggestive of this diagnosis and should prompt further investigation”

*JAMA 2007 297:23*

**Specified Entities (Cont’d)**

**Related Topic**

Exanthematous Lesions (p. 413)

Fever and Joint Pain

See JOINT PAIN AND FEVER (p. 312)

Sepsis

See SEPSIS (p. 108)
Febrile Neutropenia

IDSA Guidelines 2011

**DIFFERENTIAL DIAGNOSIS**

**BACTERIAL**
- **GRAM POSITIVE**—*S. aureus*, coagulase-negative staphylococci, *Streptococcus pneumoniae*, corynebacterium
- **GRAM NEGATIVE**—*Enterobacter*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas*, *C. difficile*, anaerobes

**VIRAL**—HSV, VZV, CMV, EBV, HHV6, enterovirus, RSV, influenza and other respiratory viruses

**FUNGAL**—*Candida*, *Aspergillus*, *Cryptococcus*, *Fusarium*

**REACTIVATION OF LATENT INFECTION**—*Histoplasma*, *Coccidioides*, *Toxoplasma*, tuberculosis

**PATHOPHYSIOLOGY**

**DEFINITION**—single temp ≥38.3 °C [101 °F] or ≥38 °C [100.4 °F] for >1 h, ANC <0.5 × 10^9/L or <1.0 × 10^9/L + expected nadir <0.5 × 10^9/L

**ABSOLUTE NEUTROPHIL COUNT (ANC)**—neutrophils + bands

**PATHOGENESIS**—chemotherapy-induced injury to mucosal barriers, immune defects due to drugs or underlying disease and invasive devices. With the attenuated immune response, patients may be relatively asymptomatic until they decompensate due to overwhelming infection. Fever is sometimes the only warning sign and should always be taken seriously in patients at risk of developing neutropenia

**NEUTROPENIA-ASSOCIATED FEBRILE EPISODES**—most commonly idiopathic; bacterial source identified in approximately 30% of episodes, usually from patient’s own endogenous flora. Fungal infections replace bacterial infections in prominence after 7 days. Fever usually abates with return of neutrophils. If fever persists or returns after neutropenia resolves, consider hepatosplenic candidiasis

**CLINICAL FEATURES**

**HISTORY**—patients usually asymptomatic other than fever. Determine severity and duration of fever, associated signs and symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache, rash), recent chemotherapy (nadir of neutrophil counts usually 10–14 days post-treatment), weight loss, night sweats, travel history, sexual history, immunizations, past medical history (malignancy, rheumatologic disorders), medications (chemotherapy, GCSF)

**PHYSICAL**—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution). Important sites to examine include venous access devices, sinuses, and perianal region for abscess. Digital rectal examination is not recommended as potential rectal tear and translocation of gut microbes (also avoid rectal thermometers, enemas, suppositories)

**MANAGEMENT**

**LOW RISK** [ANC >0.1 × 10^9/L, peak temperature <39 °C [102.2 °F], no significant symptoms or signs, no significant comorbidities, nearly normal renal and hepatic function, neutropenia ≤7 days, no dehydration, no hypotension, age <60 years]—
* ciprofloxacin 500 mg PO BID + amoxicillin–clavulinate 500 mg PO q8h.
* Send home with follow-up

**HIGH RISK** (anticipated prolonged >7 days duration and profound neutropenia [ANC ≤0.1 × 10^9/mL] and/or significant medical comorbid conditions such as hypotension, pneumonia, new-onset abdominal pain, or neurologic changes)—admit for intravenous antibiotics
- **FIRST LINE**—one of *imipenem* 500 mg IV q6h, *meropenem* 2 g IV q8h, *ceftazidime* 2 g IV q8h, *cefepime* 2 g IV q8h, *piperacillin/tazobactam* 4.5 g IV q8h, *piperacillin* 3 g IV q4h plus *tobramycin* 2–2.5 mg/kg IV q8h, *clindamycin* 600 mg

**INVESTIGATIONS**

**BASIC**
- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—blood C&S × 2 (culture peripheral blood in addition to central line ports), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, *C. difficile* toxin (if diarrhea)
- **IMAGING**—CXR
- **SPECIAL**
  - **SINUS X-ray**
IV q8h plus tobramycin 7 mg/kg IV q24h, or piperacillin/tazobactam 4.5 g IV q8h plus gentamicin 2–2.5 mg/kg IV q8h
• SECOND LINE—add vancomycin 1 g IV q12h if suspect line infection, known colonization MRSA, Gram-positive blood culture, or hypotension
• THIRD LINE—add antifungal if febrile after 4–7 days and hemodynamically unstable (fluconazole 400 mg IV daily, itraconazole 200 mg IV daily, amphotericin B 0.5–1 mg/kg IV daily over 4 h, caspofungin 70 mg on first day followed by 50 mg IV daily)
• Unexplained persistent fever in a patient whose condition is otherwise stable rarely requires an empirical change to the initial antibiotic regimen. If an infection is identified, antibiotics should be adjusted accordingly

**GCSF SUPPORT**—see TREATMENT ISSUES below

**CATHETER REMOVAL**—necessary for most patients with bacteremia/candidemia with organisms other than coagulase-negative Staphylococci

**TREATMENT ISSUES**

**MODIFICATION OF THERAPY DURING FIRST WEEK OF TREATMENT**
• IF PATIENT BECOMES AFEBRILE IN 3–5 DAYS
  • KNOWN ORGANISM—switch to specific antibiotics
  • UNKNOWN ETIOLOGY AND LOW RISK—switch to ciprofloxacin plus amoxicillin–clavulanate after afebrile for 48 h
  • UNKNOWN ETIOLOGY AND HIGH RISK—continue same antibiotics
• IF PERSISTENT FEVER DURING FIRST 3–5 DAYS
  • CLINICALLY STABLE BY DAY 3—continue antibiotics, stop vancomycin if cultures negative
  • PROGRESSIVE DISEASE BY DAY 3—change antibiotics
  • FEBRILE AFTER DAY 5—add antifungal

**DURATION OF ANTIBIOTIC TREATMENT**
• IF AFEBRILE BY DAY 3
  • STOP ANTIBIOTICS—if (1) ANC ≥0.5 × 10^9/L for 2 consecutive days, afebrile for ≥48 h, cultures negative, and no obvious signs of infection, or if (2) ANC <0.5 × 10^9/L by day 7, but afebrile for 5–7 days, patient initially at low risk, and no subsequent complications
  • CONTINUE ANTIBIOTICS—if above criteria not met

**TREATMENT ISSUES (CONT’D)**
• IF PERSISTENT FEVER ON DAY 3
  • STOP ANTIBIOTICS—if ANC ≥0.5 × 10^9/L for 4–5 consecutive days
  • CONTINUE ANTIBIOTICS—if ANC <0.5 × 10^9/L, reassess and continue antibiotics for 2 weeks. Consider stopping therapy if no disease site is found and condition is stable

**PRE-MEDICATIONS FOR AMPHOTERICIN B**
  • meperidine 50 mg IV, acetaminophen 2 tabs PO, hydrocortisone 25 mg IV 30 min before dose, and repeat × 1 1–2 h after administration

**ASCO 2006 GUIDELINE FOR GCSF USE**
• PRIMARY PROPHYLAXIS—GCSF is recommended for the prevention of febrile neutropenia if
  • HIGH-RISK PATIENTS—based on age (>65), medical history (poor performance status, previous febrile neutropenia, extensive prior treatment, poor nutrition, open wounds, active infections), disease characteristics (bone marrow involvement), and myelotoxicity of the chemotherapy regimen (chemoradiation)
  • CHEMOTHERAPY REGIMENS—20% or higher risk of febrile neutropenia or dose dense regimens
• SECONDARY PROPHYLAXIS—GCSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (in which primary prophylaxis was not received), in which a reduced dose may compromise disease-free survival overall survival, or treatment outcome
• TREATMENT OF PATIENTS WITH FEBRILE NEUTROPENIA—GCSF should be given to those with high risk of developing complications, including expected prolonged (>10 days) and profound (<0.1 × 10^9/L) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of the development of fever
• SPECIAL SITUATIONS
  • STEM CELL TRANSPLANT—to mobilize peripheral blood progenitor cell often in conjunction with chemotherapy. Also administered after autologous, but not allogeneic stem cell transplantation
  • DLBCL—prophylactic GCSF should be given for patients with diffuse aggressive lymphoma age 65 and older treated with
curative chemotherapy (CHOP or more aggressive regimens)

- **AML**—may be given shortly after completion of the initial induction chemotherapy to modestly decrease the duration of neutropenia
- **ALL**—recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post-remission course, thus shortening the duration of neutropenia by approximately 1 week
- **MDS**—may be used to increase the ANC in neutropenic patients. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infections
- **POST-RADIATION**—GCSF should be given to patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs

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**SPECIFIC ENTITIES**

**NECROTIZING ENTEROCOLITIS** (typhlitis)

- **PATHOPHYSIOLOGY**—mucosal injury in patients with profound neutropenia → impaired host defense → necrosis of bowel wall, involving cecum extending into ascending colon and terminal ileum
- **CLINICAL FEATURES**—abdominal pain (especially RLQ) in neutropenic patients
- **DIAGNOSIS**—CT abd. Avoid barium enema and colonoscopy
- **TREATMENTS**—bowel rest, NG suction, IV fluids, nutritional support, broad spectrum antibiotics, GCSF. Surgical indications include peritonitis, perforation, persistent GI bleeding, or clinical deterioration

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**DIFFERENTIAL DIAGNOSIS**

**FEVER WITH CNS INVOLVEMENT**

- **BACTERIAL**—meningococcal, typhoid fever, rickettsial, leptospirosis
- **MYCOBACTERIAL**—tuberculosis
- **VIRAL**—Japanese encephalitis, West Nile encephalitis, tick-borne encephalitis, poliomyelitis, rabies
- **FUNGAL**—coccidioidomycosis
- **PARASITIC**—malaria, angiostrongyliasis, trypanosomiasis

**FEVER WITH RESPIRATORY INVOLVEMENT**

- **BACTERIAL**—S. pneumoniea, mycoplasma, Legionella, Q fever, typhoid fever, scrub typhus
- **MYCOBACTERIAL**—tuberculosis
- **VIRAL**—influenza, parainfluenza, metapneumovirus, respiratory syncytial virus, adenovirus, dengue, coronavirus
- **FUNGAL**—histoplasmosis, coccidioidomycosis
- **PARASITIC**—malaria, Loeffler’s syndrome (migration of larval helminths such as ascaris, strongyloides, and hookworm)

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**ACUTE TRAVELER’S DIARRHEA ± FEVER**

- **BACTERIAL**—Enterotoxigenic or enterogauggerative E. coli, Campylobacter jejunii, Salmonella, Shigella, Vibrio, Aeromonas, Plesiomonas, C. difficile
### Differential Diagnosis (Cont’d)

- **Viral**—Caliciviruses (Norwalk, Norwalk-like), rotaviruses, Ebola fever, enteroviruses
- **Parasitic**—Giardia lamblia, Cryptosporidium parvum, Entamoeba histolytica, Cyclospora cayetanensis, Isospora belli, E. polecki, Balantidium coli, Trichinella spiralis

### Chronic Traveler’s Diarrhea ± Fever

- **Bacterial**—Enterogauggregative or enteropathogenic E. coli, C. jejuni, Shigella, Salmonella, Yersinia enterocolitica, Aeromonas, Plesiomonas, C. difficile, Tropheryma whippelii
- **Mycobacterial**—tuberculosis, M. avium complex
- **Fungal**—Paracoccidioides brasiliensis, Histoplasma capsulatum
- **Parasitic**—*G. lamblia*, *E. histolytica*, Cryptosporidium parvum, *C. cayetanensis*, Trichuris trichiura, Strongyloides stercoralis, Schistosomiasis, Capillaria philippinensis, Fasciolopsis buski, Metagonimus yokogawai, Echinostoma
- **Non-Infectious**—small-bowel overgrowth syndrome, disaccharidase deficiency, tropical sprue, irritable bowel syndrome, inflammatory bowel disease, cancer, laxative use, endocrinopathy, dysmotility, idiopathic

### Investigations (Cont’d)

| Investigation |
|--------------|
| **DIFFERENTIAL DIAGNOSIS** (CONT’D) |
| **BASIC** |
| Labs—CBCD, lytes, Cr, AST, ALT, ALP, bilirubin, urinalysis |
| Microbiology—blood CS, sputum Gram stain/AFB/C&S, urine CS, stool C&S, O&P, C. |

### Pre-Travel Considerations

**Vaccinations**—standard regardless of travel (influenza, pneumococcal if age >65, hepatitis B, MMR, DPT), developing countries (hepatitis A), specific countries (meningococcal, Japanese encephalitis, yellow fever), high-risk activity (rabies), outbreaks (cholera)

**Malaria Prophylaxis**—see below

### Special

**Lumbar Puncture**

**DIFFERENTIAL DIAGNOSIS**—see below

**DIARRHEA PROPHYLAXIS**—ciprofloxacin and imodium if diarrhea develops

### Specific Entities

**PRIORITY**—focus on those illnesses that are potentially fatal or may be public health threats

**Top Travel-Related Infections**—malaria, typhoid fever, dengue fever, diarrheal disease, respiratory infections, Lyme disease, Q fever, brucellosis

**Malaria**—the most important cause of fever in returning travelers. *P. falciparum* can be rapidly fatal and must be ruled out in all febrile travelers returning from malaria-endemic regions. It has the shortest incubation period and >90% of affected travelers will become ill within 30 days of return

**Pathophysiology**—anopheline mosquito bite transmits sporozoites → travel to liver and invade hepatocytes → divide and form schizonts which contain merozoites (asymptomatic) → rupture after 6–16 days and release merozoites into the bloodstream → infect erythrocytes and mature from ring forms to trophozoites to mature schizonts (sexual form) over 48 (*P. vivax*, *P. ovale*, *P. falciparum*) or 72 (*P. malariae*) hours → merozoites released from erythrocytes (fever, anemia, lactic acidosis, cytokine release) and infect new red cells → few merozoites differentiate into male or female gametocytes (sexual forms) can circulate in blood until ingested by mosquito. *P. vivax* and *P. ovale* may stay dormant in the liver as hypnozoites and may cause late relapse by reactivating after many months. In contrast, *P. falciparum* and *P. malariae* have no liver stage and do not
SPECIFIC ENTITIES (CONT’D)

cause relapse. *P. falciparum* specifically can induce obstruction of microvascular blood flow, and may lead to organ dysfunction (e.g. cerebral malaria, renal failure, ARDS, hypoglycemia, anemia, DIC, and gastroenteritis)

- **CLINICAL FEATURES**—*P. falciparum* is acquired mostly from sub-Saharan Africa, while *P. vivax* is mostly from Asia or Latin America. Symptoms include spiking fevers, chills, headache, back pain, cough, GI problems. Splenomegaly and thrombocytopenia without leukocytosis may be present. Cerebral malaria (*P. falciparum*) presents as altered level of consciousness or seizures and is universally fatal if untreated
- **DIAGNOSIS**—thick and thin smear (need to repeat over 48 h to rule out malaria)
- **PROPHYLAXIS**—the relative risk of contracting malaria varies by geographic region: Caribbean 4, North Africa 7, South America 8, Southeast Asia 12, Central America 38, South Asia 54, Oceania 77, and sub-Saharan Africa 208. Travelers should be advised to wear long sleeves/pants between dusk and dawn, use mosquito repellents containing 30–50% DEET, and consider permethrin-treated mosquito nets. Chloroquine may be used for travel to destinations with chloroquine-sensitive *P. falciparum* (e.g. most of Central America and parts of the Middle East). For destinations where chloroquine-resistant *P. falciparum* is present, chemoprophylaxis with atovaquone–proguanil, mefloquine, or doxycycline should be used. Give atovaquone–proguanil or doxycycline for travel to destinations with *P. falciparum* resistance to chloroquine, mefloquine, and sulfonamides (e.g. regions of Thailand, Cambodia, China, Laos, and Vietnam). Atavaquone–proguanil associated with fewest side effects. Mefloquine has ease of weekly dosing. Doxycycline is the cheapest, but requires prolonged course and causes sun sensitization. CDC 2010 risk assessment and prophylaxis recommendations are available online at [http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria-risk-information-and-prophylaxis.aspx](http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria-risk-information-and-prophylaxis.aspx)
- **TREATMENTS**—artesunate has emerged as the treatment of choice for complicated malaria. Other options include quinine–doxycycline, atovaquone–proguanil, and mefloquine. Chloroquine–primaquine for non-falciparum

**NEJM 2008 359:6**
[www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s1/index-eng.php](www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s1/index-eng.php)

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**SPECIFIC ENTITIES (CONT’D)**

**TYPHOID FEVER**

- **PATHOPHYSIOLOGY**—acquired after exposure to food or water contaminated by *Salmonella typhi*
- **CLINICAL FEATURES**—mainly in developing countries. Fever, chills, headache, myalgia, abdominal pain and constipation (uncommonly diarrhea), relative bradycardia, splenomegaly, and rose spots (faint salmon-colored macules on the abdomen and trunk). Septic symptoms from intestinal perforation may occur in second week
- **DIAGNOSIS**—blood, stool, urine, or bone marrow (highest sensitivity) culture; CBC may show leukopenia
- **TREATMENTS**—fluoroquinolones, ceftriaxone, azithromycin

**DENGUE FEVER** (break-bone fever)

- **PATHOPHYSIOLOGY**—flavivirus transmitted by mosquito → flu-like illness 4–7 days later → may develop lymphadenopathy, maculopapular/petechial rash → dengue shock syndrome and dengue hemorrhagic fever if previously exposed to other serotypes
- **CLINICAL FEATURES**—acquired mostly from tropical and subtropical areas. Fever, headache, retro-orbital pain, severe myalgia/arthritis. Leukopenia and thrombocytopenia
- **DIAGNOSIS**—serology
- **TREATMENTS**—supportive

**EBOLA FEVER**

- **EPIDEMIOLOGY**—flavivirus possibly transmitted by fruit bats → person to person transmission occurs from direct contact with blood or bodily fluids (saliva, blood, vomit, stool or semen) of infected symptomatic patients. Incubation period is 2–21 days. 2014 outbreaks in Sierra Leon, Guinea, and Liberia
- **CLINICAL FEATURES**—early symptoms include fever, headache, myalgia/arthritis, vomiting, diarrhea, abdominal pain, conjunctival injection, and rash. Late symptoms include bleeding, shock, delirium and death
- **DIAGNOSIS**—high index of suspicion if patient has recently been in endemic area during an Ebola outbreak. Serology (sens 91%) and RT-PCR (sens close to 100%, spc 97%)
- **TREATMENTS**—rapid isolation. Supportive measures are the mainstay. An experimental therapy, ZMapp, consists of 3 monoclonal antibodies against Ebola viral antigens. Its efficacy has not been proven

**CHIKUNGUNYA FEVER**

- **PATHOPHYSIOLOGY**—mosquito-borne viral infection acquired in Africa and Asia. Large outbreaks ongoing in Indian Ocean islands and India
CLINICAL FEATURES—fever (usually within 2–4 days of exposure) with severe joint pains involving small joints of hands, wrists, and ankles; may be prolonged. Leukopenia, thrombocytopenia, and elevated transaminases may be seen.

DIAGNOSIS—serology (acute and convalescent)

TREATMENTS—symptomatic with NSAIDs

RICKETTSIAL INFECTIONS (OUTSIDE OF NORTH AMERICA)

PATHOPHYSIOLOGY—African tick typhus (Rickettsia africae), Mediterranean tick typhus (R. conorii), and scrub typhus (Orientia tsutsugamushi) are all transmitted by ticks.

CLINICAL FEATURES—tick bite ± inoculation eschar with a triad of fever, headache, and myalgia. Rash may be present. Lymphadenopathy, leukopenia, and thrombocytopenia.

DIAGNOSIS—serology

TREATMENTS—doxycycline

RICKETTSIAL INFECTIONS (WITHIN OF NORTH AMERICA)

PATHOPHYSIOLOGY—Leptospirosis

CLINICAL FEATURES—transmitted by drinking or eating infected animal products (milk), inhalation, or direct animal contact through skin wounds. Other than fever, may involve any organ system, particularly joints (sacroiliitis), GU (epididymo-orchitis), CNS (meningitis), eyes (uveitis), cardiac (endocarditis), pulmonary (pneumonitis, pleural effusion, empyema), and can cause abscesses (hepatic, splenic, thyroid, epidural). May develop into chronic hepatosplenic disease.

DIAGNOSIS—blood cultures, serology

TREATMENTS—doxycycline plus streptomycin or rifampin

SCHISTOSOMIASIS

PATHOPHYSIOLOGY—trematode worms S. haematobium, S. mansoni, S. intercalatum in sub-Saharan Africa, S. mansoni in part of South America, S. japonicum in Asia, S. mekongi in Cambodia. Freshwater exposure → cercariae penetrate skin → larvae migrate to lung through venous circulation → migrate to heart → migrate to liver, where they mature and pair off → migrate to mesenteric venules of bowel (S. mansoni, mekongi, japonicum, and intercalatum) bladder (S. hematobium), where females lay eggs → excreted into feces or urine → mature to cercariae

CLINICAL FEATURES—this parasitic infection is generally seen in patients from endemic areas instead of travelers. Initial penetration of skin may cause pruritus. Acute schistosomiasis (Katayama fever) includes fever, headache, myalgias, RUQ pain, bloody diarrhea, and dyspnea. Chronic schistosomiasis with granuloma formation is due to host's immune response to schistosome eggs, leading to hepatic (cirrhosis), intestinal (diarrhea, occult blood, fibrosis) or genitourinary tract symptoms (hematuria, dysuria, calcification, fibrosis), and rarely CNS (seizures, focal deficit, transverse myelitis) involvement.

DIAGNOSIS—serology, schistosome eggs in feces or urine, biopsy of rectum or bladder

TREATMENTS—praziquantel 20 mg/kg PO q8h × 2 doses (3 doses for S. japonicum and mekongi); adjunctive corticosteroids for Katayama fever

SPECIFIC ENTITIES (CONT’D)

Pneumonia

See PNEUMONIA (p. 7)

Endocarditis

See ENDOCARDITIS (p. 60)
**Meningitis**

**Differential Diagnosis for Fever and Neurological Symptoms**

**DIMS**
- **Drugs**—neuroleptic malignant syndrome, serotonin syndrome, sympathomimetics, alcohol withdrawal
- **Infectious**
  - **Meningitis**—bacterial (S. pneumoniae, N. meningitidis, H. influenzae, L. monocytogenes, Klebsiella, E. coli, Serratia, Pseudomonas), viral (enterovirus, VZV, influenza, mumps, HIV), TB, fungal (Cryptococcus)
  - **Encephalitis**—HSV, West Nile, St. Louis, Equine, La Crosse
  - **Abscess**—bacterial
- **Metabolic**—thyroid storm

**Structural**
- **Hemorrhage**—subarachnoid, epidural, subdural, intracerebral
- **Cerebral Infarct**
- **Tumor**
- **Pituitary Aplasia**
- **Vascular**—TTP/HUS, lupus, vasculitis, granulomatous angiitis

**Pathophysiology (Cont’d)**

**Associations with Specific Organisms**
- **Age 0–4 weeks**—S. agalactiae, E. coli, Listeria monocytogenes, K. pneumoniae
- **Age 1–23 months**—S. agalactiae, E. coli, S. pneumoniae, H. influenzae, N. meningitidis
- **Age 2–50 years**—S. pneumoniae, N. meningitidis, L. monocytogenes, aerobic Gram-negative bacilli*
- **Immunocompromised**—Listeria, aerobic Gram negative bacilli*
- **Neurosurgery/Head Trauma**—S. aureus, S. epidermidis, aerobic Gram-negative bacilli*
- **CSF Shunt**—S. aureus, S. epidermidis, aerobic Gram negative bacilli*, diphtheroids
- **Basilar Skull Fracture**—S. pneumoniae, H. influenzae, group A Streptococci

*R aerobic Gram-negative bacilli include Klebsiella, E. coli, Serratia, and Pseudomonas

**Risk Factors for S. Pneumoniae**—pneumonia, otitis media, mastoiditis, sinusitis, endocarditis, head trauma with CSF leak, alcoholism, splenectomy

**Risk Factors for L. Monocytogenes**—extremes of age, alcoholism, malignancy, immunosuppression, diabetes, hepatic failure, renal failure, iron overload, collagen vascular disease, HIV

**Complications**—neurologic complications include hemiation, stroke, vasculitis, acute cerebral hemorrhage, and aneurysm formation of cerebral vessels, with symptoms such as seizures, hearing loss, and neuropsychological impairment. Systemic complications include septic shock, pneumonia, and ARDS

**Clinical Features**

**Rational Clinical Examination Series: Does This Adult Patient Have Acute Meningitis?**

|         | Sens (%) | Spc (%) |
|---------|----------|---------|
| History |          |         |
| Headache| 68       |         |
| Nausea and vomiting | 52 |         |
| Neck pain | 28 |         |
| Physical |          |         |
| Fever | 87       |         |
| Neck stiffness | 80 |         |
| Altered mental status | 69 |         |
| Focal neurological findings | 21 |         |
| Rash | 13       |         |
| Kernig sign (patient lying supine with hip flexed >90°. Extension of knee from this position elicits resistance or pain in lower back or posterior thigh) | 9 | 100 |
### CLINICAL FEATURES (CONT’D)

| Sens (%) | Spc (%) |
|----------|---------|
| Brudzinski sign (passive neck flexion in supine patient results in flexion of knees and hips) | – | – |
| Jolt accentuation of headache (patient turns head horizontally at a frequency of 2–3 rotations per second. Worsening headache represents positive sign) | 97 | 60 |

### Combination of Findings

- Classic triad (fever, neck stiffness, headache) 46

**UPDATE**—individual findings are not sufficiently accurate to diagnose meningitis. Absence of all 3 signs of the classic triad of fever, neck stiffness, and altered mental status is not sufficiently sensitive to rule out a diagnosis of meningitis. Fever and neck stiffness are the most sensitive findings of the triad. Kernig and Brudzinski signs have low sensitivity but high specificity. Jolt accentuation of headache may be a useful adjunctive maneuver for patients with fever and headache but requires further validation.

*JAMA 1999 282:2*

*The Rational Clinical Examination. McGraw-Hill, 2009*

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### INVESTIGATIONS

#### BASIC
- **LABS**—CBCD, lytes, Cr/urea, INR, PTT, AST, ALT, ALP, bilirubin, fibrinogen, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S
- **IMAGING**—CXR, head CT (see below)
- **LUMBAR PUNCTURE**—(1) cell count and differential; (2) Gram stain, C&S and AFB; (3) cell count and differential; (4) protein, glucose, lactate; (5) PCR for HSV, VZV, enteroviruses; (6) cytology

#### DIAGNOSTIC AND PROGNOSTIC ISSUES

**LUMBAR PUNCTURE**—suspect bacterial infection if high neutrophils, low glucose, high protein, positive culture. Suspect viral infection if high lymphocytes, normal glucose, and normal/high protein *(NEJM 2006 355:e12)*

- **OPENING PRESSURE**—normal is 60–250 mmHg. Causes of elevated opening pressure include meningitis, pseudotumor cerebri, intracranial hemorrhage, tumors, and idiopathic
- **CELL COUNT AND DIFFERENTIAL**—normal WBC is <5/mm³. This can increase to 1000–5000/mm³ for bacterial meningitis (neutrophils mainly) and 50–1000/mm³ for viral meningitis (lymphocyte predominant). Other causes include seizure, intracerebral hemorrhage, tumor, and “traumatic tap” (correct by +1 WBC for every 500–1000 RBCs)
- **XANTHOCHROMIA**—lysed RBCs. Present in >90% of patients within 12 h of subarachnoid hemorrhage onset
- **GRAM STAIN**—sensitivity is 60–80% in untreated bacterial meningitis and 40–60% in partially treated cases
- **CULTURE**—gold standard with sensitivity of 70–85% in untreated bacterial meningitis and 50% in partially treated cases. Viral, TB, and fungal cultures may be done as well
- **PROTEIN**—normal is 0.18–0.58 g/L. Significantly elevated in bacterial meningitis and obstruction, variably elevated in fungal and TB infections, and only sometimes elevated in viral infections. Other causes include tumors, intracranial hemorrhages, multiple sclerosis, and Guillain–Barre syndrome
- **GLUCOSE**—normal is 2/3 of serum level, up to 16.7 mM [300 mg/dL]. Significantly lower in bacterial meningitis, mildly lower in fungal and TB infections, and usually normal in viral infections

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**DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT’D)**

| Brudzinski sign (passive neck flexion in supine patient results in flexion of knees and hips) | – | – |
| Jolt accentuation of headache (patient turns head horizontally at a frequency of 2–3 rotations per second. Worsening headache represents positive sign) | 97 | 60 |

**UPDATE**—individual findings are not sufficiently accurate to diagnose meningitis. Absence of all 3 signs of the classic triad of fever, neck stiffness, and altered mental status is not sufficiently sensitive to rule out a diagnosis of meningitis. Fever and neck stiffness are the most sensitive findings of the triad. Kernig and Brudzinski signs have low sensitivity but high specificity. Jolt accentuation of headache may be a useful adjunctive maneuver for patients with fever and headache but requires further validation.

*JAMA 1999 282:2*

*The Rational Clinical Examination. McGraw-Hill, 2009*
RATIONAL CLINICAL EXAMINATION SERIES: HOW DO I PERFORM A LUMBAR PUNCTURE AND ANALYZE THE RESULTS TO DIAGNOSE BACTERIAL MENINGITIS?

TECHNIQUE—“use of an atraumatic needle compared with a standard needle and use of a 26-gauge standard needle compared with a 22-gauge standard needle have been shown to be associated with reduced risk of headache after lumbar puncture. Reinsertion of the stylet before needle removal should occur (ARR 11%). Patients do not require bed rest after the procedure”

CT HEAD—indicated before lumbar puncture only if age >60, immunocompromised, history of CNS disease, seizures within 1 week, focal neurological abnormalities, papilloedema, obtunded or unconscious, inability to answer two questions correctly, or inability to follow two commands correctly

PROGNOSIS—mortality rate is 19–26% for *S. pneumoniae* meningitis and 3–13% for *N. meningitidis* meningitis. Factors conferring poor prognosis include systemic compromise, ↓ level of consciousness, and *S. pneumoniae*

MANAGEMENT

ACUTE—ABC, O₂, IV, intubation. Droplet precautions for suspect *N. meningitidis* infection

EMPIRIC ANTIBIOTICS—steroid if acute bacterial meningitis and 15–20 min before first dose of antibiotics (dexamethasone 0.15 mg/kg or 10 mg IV q6h × 4 days). *Cefotaxime* 2 g IV q6h or *ceftriaxone* 2 g IV q12h. Add *vancomycin* 500–750 mg IV q6h if concerned about penicillin-resistant Pneumococci. Add *ampicillin* 2 g IV q4h if age >50 for *Listeria* coverage. If neurosurgery/trauma, CSF shunt, or basilar skull fracture, give *cefazidime* 2 g IV q8h plus *vancomycin*. If HSV encephalitis, give *acyclovir* 10 mg/kg IV q8h

SPECIFIC ANTIMICROBIAL THERAPIES—*S. pneumoniae* (penicillin G or ampicillin if MIC <0.1 μg/mL, ceftriaxone or cefotaxime ± *vancomycin* × 10–14 days if MIC >1.0 μg/mL), *N. meningitidis* (ceftriaxone, penicillin G or ampicillin × 7 days), *L. monocytogenes* (ampicillin or penicillin G, plus gentamicin × 21 days), *H. influenzae* (ampicillin, ceftriaxone, or cefotaxime × 7 days), *Enterobacteriaceae* (ceftriaxone or cefotaxime × 7 days)

SPECIFIC ENTITIES

CHRONIC MENINGITIS (>4 weeks symptoms and persistent CSF abnormalities)—consider TB, fungal infections, neurosarcoïdosis, lymphoma, and leptomeningeal carcinomatosis

RECURRENT MENINGITIS—congenital predisposition (myelomeningocele, dermal sinus), acquired (trauma, tumor, shunt), immunologic defects (complement defects, antibody defects, splenectomy)

HSV ENCEPHALITIS

• PATHOPHYSIOLOGY—usually infects the temporal lobe → subacute illness with fever, focal neurologic abnormalities, aphasia, mental status changes, and seizures. May have long-term sequelae

• DIAGNOSIS—lumbar puncture (mild lymphocytic pleocytosis <500 cells/μL, erythrocytes, xanthochromia, ↑ protein, normal glucose, PCR for HSV1 and HSV2), MRI (hyperintense lesion in the inferior medial temporal lobe, often extending into the insula)

• TREATMENTS—*acyclovir* 10 mg/kg/dose q8h × 14–21 days

WEST NILE VIRUS ENCEPHALITIS

• PATHOPHYSIOLOGY—flavivirus West Nile virus transmitted by mosquitoes between late spring and early autumn

• CLINICAL FEATURES—wide spectrum from asymptomatic (30%) to severe neurologic disorder (0.5%). Fever, erythematous rash, meningitis, encephalitis, and flaccid paralysis.
Risk of progression to severe neurological disease about 1/150, highest in the elderly

- **DIAGNOSIS**—lumbar puncture (viral picture, PCR for West Nile virus), IgM antibody to West Nile virus in serum or cerebrospinal fluid (samples from the acute and convalescent phases, submitted at least 2 weeks apart)

- **TREATMENTS**—supportive. Prevention is key (insect repellent, proper clothing)

**Related Topics**
- Delirium (p. 432)
- Infection Control (p. 304)

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**DIFFERENTIAL DIAGNOSIS OF DYSURIA**

★ SUV ★

**Sexually transmitted diseases**—Chlamydia trachomatis, Neisseria gonorrhoeae, HSV

**Urinary tract infections** (urethritis, cystitis, pyelonephritis, perinephric abscess)—**bacterial**

(★ KEEPS ★ Klebsiella, E. coli, Enterococci, Proteus, Staphylococcus saprophyticus)

**Vaginal infections**—Candida albicans, Trichomonas, bacterial vaginosis

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**PATHOPHYSIOLOGY OF URINARY TRACT INFECTIONS**

**Complicated UTI**—presence of functional or anatomic abnormality of the urinary tract (polycystic kidney disease, nephrolithiasis, neurogenic bladder, diabetes, immunosuppression, pregnancy, indwelling urinary catheter, recent urinary tract instrumentation)

**Uncomplicated UTI**—absence of risk factors above. In women, uncomplicated UTIs are usually treated for 3 days (or 5–7 days with nitrofurantoin)

**Pyelonephritis**—usually 18–40-year-old women, fever, costovertebral angle tenderness, blood and urine cultures indicated. Challenges differentiating between cystitis and pyelonephritis

**Risk factors for UTI**

- **Young women**—frequent or recent sexual activity

- **Elderly women**—age, estrogen deficiency, incontinence, diabetes, cystoceles, previous GU surgery

**Pathophysiology of catheter-associated bacteriuria**—bacteria establish biofilm in or on catheter and enter bladder

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**Pathophysiology of urinary tract infections (cont’d)**

Intra- or extraluminally. Common organisms include *E. coli* and enterococci. Responsible for 80% of urosepsis. Risk factors include duration of catheterization, errors in catheter care, diabetes mellitus, and female sex

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**Clinical features of urinary tract infections**

RATIONAL CLINICAL EXAMINATION SERIES:

**Does this woman have acute UTI?**

| Symptom                  | LR+ | LR- |
|--------------------------|-----|-----|
| Dysuria                  | 1.5 | 0.5 |
| Frequency                | 1.8 | 0.6 |
| Hematuria                | 2.0 | 0.9 |
| Fever                    | 1.6 | 0.9 |
| Flank pain               | 1.1 | 0.8 |
| Lower abdominal pain     | 1.1 | 0.9 |
| Vaginal discharge        | 0.3 | 3.1 |
| Vaginal irritation       | 0.2 | 2.7 |
| Back pain                | 1.6 | 0.8 |

**Physical**

- Vaginal discharge: 0.7 ± 1.1
- CVA tenderness: 1.7 ± 0.9

**Urine dipstick**

- Leukocyte esterase or nitrite positive: 4.2 ± 0.3

**Approach**—“four symptoms (dysuria, frequency, hematuria, back pain) and one sign (CVA tenderness) increased the probability of UTI and may effectively rule in if all present. However, no combinations reliably rule out UTI. Urinalysis is moderately powerful and should be considered in women with appropriate urinary tract
CLINICAL FEATURES OF URINARY TRACT INFECTIONS (CONT’D)
symptoms. If the dipstick leukocyte esterase or nitrite is positive, the probability of UTI is high, especially when combined with other positive findings from the history and physical. If dipstick is negative but probability of disease is still relatively high, a urine culture should be considered to rule out infection”

JAMA 2002 287:20
The Rational Clinical Examination.
McGraw-Hill, 2009

INVESTIGATIONS FOR URINARY TRACT INFECTIONS

BASIC
- LABS—CBCD, lytes, Cr/urea, urinalysis
- MICROBIOLOGY—urine C&S

DIAGNOSTIC ISSUES FOR URINARY TRACT INFECTIONS

NUMBER OF BACTERIA—significant bacteria (>10⁵/mL) in clean catch suggests UTI (sens 50%). If using lower threshold to >10³/mL for women with symptoms, sensitivity increases and specificity only decreases slightly

URINALYSIS—nitrite or leukocyte esterase (sens 75%, spc 82%), pyuria (sens 95%, spc 71%), bacteria (sens 40–70%, spc 85–95%). Not necessary if symptomatic uncomplicated UTI

URINE CULTURE—not always needed if symptomatic and biochemical evidence (i.e. leukocyte esterase) of uncomplicated UTI (see Clinical Features). However, antimicrobial resistance is increasing, so culture and sensitivity may become more important

MANAGEMENT OF URINARY TRACT INFECTIONS (CONT’D)

tab PO qhs × 6 months, nitrofurantoin 50 mg or macrocrystals 100 mg PO qhs × 6 months), post-coital prophylaxis (trimethoprim–sulfamethoxazole DS ½–1 tab PO post-coital, nitrofurantoin 50 mg PO or macrocrystals 100 mg PO post-coital), patient-initiated treatment (start standard dose of antibiotics with onset of UTI symptoms)

SYMPTOM CONTROL—phenazopyridine 100–200 mg PO TID × 2 days

ACUTE UNCOMPPLICATED PYELONEPHRITIS—
treat empirically with oral fluoroquinolones × 7 d (ciprofloxacin 500 mg PO BID or levofloxacin 750 mg PO daily). If isolate susceptible, may treat with trimethoprim–sulfamethoxazole, amoxicillin, or amoxicillin–clavulanate × 14 d. Most otherwise healthy, non-pregnant women with pyelonephritis can be treated on an outpatient basis. Otherwise, treat with IV antibiotics, at least initially (aminoglycoside ± ampicillin, third generation cephalosporin, or carbapenem)

CATHETER-ASSOCIATED BACTERIURIA—
remove or replace catheter and initiate antibiotics for symptomatic infection; switch to intermittent catheterization

PREGNANCY AND UTI—urinalysis for all pregnant women at 16 weeks. Treat all bacteriuria with amoxicillin or nitrofurantoin × 3–7 days even if asymptomatic as there is a 20–40% risk of pyelonephritis. Avoid fluoroquinolones

VAGINITIS

CANDIDA—vulvovaginitis with cheesy vaginal discharge, intense itch. Diagnosis by microscopy with 10% KOH showing hyphae and budding yeast, pH 4–4.5 (normal). Treat with vaginal antifungal cream (3–14 days) or fluconazole 150 mg PO × 1 dose

TRICHOMONIASIS—profuse purulent greenish vaginal discharge, strawberry cervix. Diagnosis by microscopy showing motile trichomonads, pH 5–6. Treat with oral metronidazole 2 g as a single dose (treatment of sexual partners indicated)

BACTERIAL VAGINOSIS—gray, fishy-smelling vaginal discharge. Diagnosis made by amine odor when KOH added to the discharge, pH >4.5 and clue cells (vaginal epithelial cells coated with bacteria) seen on microscopy. Treat if symptomatic or pregnant with metronidazole or clindamycin, orally or vaginally
SEXUALLY TRANSMITTED INFECTIONS (STI)

URETHRITIS IN MEN/CERVICITIS IN WOMEN

- PATHOPHYSIOLOGY — N. gonorrhoea, Chlamydia trachomatis, and other non-gonococcal (Ureaplasma urealyticum, Mycoplasma genitalium, Trichomonas vaginalis, HSV)

- DIAGNOSIS — Gram stain of discharge, urine for chlamydia/gonorrhea (nucleic acid amplification test, NAAT) or urethral/cervical swab for gonorrhea culture; offer syphilis and HIV testing

- TREATMENTS — anti-gonococcal (cefixime 400 mg PO × 1 or ceftriaxone 125 mg IM × 1 plus azithromycin 1 g PO × 1), anti-chlamydial (azithromycin 1 g PO × 1, or doxycycline 100 mg PO BID × 7 days). If gonorrhea identified, empirically treat for both gonococcus and chlamydia since dual infection is common. Dual therapy is recommended for gonorrhea due to increasing incidence of resistance to third generation cephalosporins. Trace and treat all partners within the last 60 days

SYPHILIS

- PATHOPHYSIOLOGY — Treponema pallidum infection. Risk factors include men who have sex with men (MSM), sex trade, HIV infection

- PRIMARY SYPHILIS — presents as chancre (painless, indurated, non-purulent ulcer) within 3–90 days

- SECONDARY SYPHILIS — develops within 2 weeks to 6 months, with symptoms such as fever, maculopapular rash, mucocutaneous lesions, alopecia, lymphadenopathy, meningitis, urethritis, and cranial neuritis

- TERTIARY SYPHILIS — develops after year(s) and may involve the heart (aortitis), eyes (iritis, Argyll Robertson pupil), bones/soft tissues (gummas), and neurologic system (general paresis, a rapidly progressive dementia with psychotic features and tabes dorsalis which affects posterior columns of the spinal cord and the dorsal roots, leading to pain episodes, decreased vibration and proprioception, absent reflexes, and bowel/bladder dysfunction)

- DIAGNOSIS — first-line diagnostic test of choice for a primary syphilitic chancre should be either DFA or PCR, if available. Otherwise, treponemal serologies are more sensitive and become positive earlier than non-treponemal serologies and would be preferred if primary syphilis is a consideration

| Diagnostic Method | Test(s) | Utility |
|-------------------|---------|---------|
| Direct visualization | Dark field microscopy | Traditional but availability is limited |
| Visualization with fluorescent Ab | DFA | Diagnosis of 1st syphilis |
| Molecular testing | PCR | Sensitive-specific |
| Treponemal serology (presence of Ab against TP) | FTA-ABS, TPPA, MHA-TP, TP-EIA, INNO-LIA | Diagnosis of syphilis |
| Non-treponemal serology (presence of Ab against cardiolipin/lecithin) | VDRL, RPR | Screening, RPR titer helpful in staging, check for reinfection, treatment monitoring |

Abbreviations: DFA direct fluorescent antibody, EIA enzyme immunoassay, FTA-ABS fluorescent treponemal antibody-absorption, MHA-TP microhemagglutination assay for antibody to TP, PCR polymerase chain reaction, RPR rapid plasma reagin test, TP treponema pallidium, TPPA TP particle agglutination assay, VDRL Venereal Disease Research Laboratory, INNO-LIA line immunoassay
PELVIC INFLAMMATORY DISEASE

- PATHOPHYSIOLOGY — includes endometritis, tubo-ovarian abscess, salpingitis, and pelvic peritonitis. Most commonly due to *N. gonorrhoeae*, *C. trachomatis*, *M. hominis*, *U. urealyticum*; may involve endogenous (gut) organisms including anaerobes. Complications include infertility, ectopic pregnancy, and chronic pelvic pain.

- CLINICAL FEATURES — lower abdominal pain, abnormal vaginal bleeding/discharge, and dyspareunia may be mild and non-specific. Findings include lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness.

- DIAGNOSIS — high index of clinical suspicion. Cervical swab and urine NAAT for Chlamydia and gonorrhea. Ultrasound. Pregnancy test.

- TREATMENTS — for primary, secondary and early latent (<1 year) syphilis, *benzathine penicillin G* 2.4 M units IM × 1 (preferred) or *doxycycline* 100 mg PO BID × 2 weeks. For late latent (>1 year) syphilis, gummatous and cardiovascular syphilis, *benzathine penicillin G* 2.4 M units IM q7days × 3 weeks. For neurosyphilis or syphilitic eye disease, give *benzathine penicillin G* 3–4 M units q4h IV × 10–14 days. Follow-up is essential. Treatment failure is defined as persistent symptoms or failure of serologic test to decline by 4 fold within 6 months.

INFECTIONS

- SEXUALLY TRANSMITTED INFECTIONS (STI) (CONT’D)

  - TREATMENTS — for primary, secondary and early latent (<1 year) syphilis, *benzathine penicillin G* 2.4 M units IM × 1 (preferred) or *doxycycline* 100 mg PO BID × 2 weeks. For late latent (>1 year) syphilis, gummatous and cardiovascular syphilis, *benzathine penicillin G* 2.4 M units IM q7days × 3 weeks. For neurosyphilis or syphilitic eye disease, give *benzathine penicillin G* 3–4 M units q4h IV × 10–14 days. Follow-up is essential. Treatment failure is defined as persistent symptoms or failure of serologic test to decline by 4 fold within 6 months.

  - DIAGNOSIS — high index of clinical suspicion. Cervical swab and urine NAAT for Chlamydia and gonorrhea. Ultrasound. Pregnancy test.

  - TREATMENTS — for primary, secondary and early latent (<1 year) syphilis, *benzathine penicillin G* 2.4 M units IM × 1 (preferred) or *doxycycline* 100 mg PO BID × 2 weeks. For late latent (>1 year) syphilis, gummatous and cardiovascular syphilis, *benzathine penicillin G* 2.4 M units IM q7days × 3 weeks. For neurosyphilis or syphilitic eye disease, give *benzathine penicillin G* 3–4 M units q4h IV × 10–14 days. Follow-up is essential. Treatment failure is defined as persistent symptoms or failure of serologic test to decline by 4 fold within 6 months.

  - TREATMENTS — outpatient (ceftriaxone 250 mg IM × 1 and *doxycycline* 100 mg PO BID × 14 days, or *levofloxacin* 500 mg PO daily × 14 days); add *metronidazole* 500 mg PO BID × 14 days if there are risk factors for anaerobic pathogens. Inpatient (doxycycline 100 mg PO q12h and *cefotaxime* 2 g IV q6h × 14 days, or *clindamycin* 900 mg IV q8h and *gentamicin* 1.5 mg/kg IV q8h × 14 days)

http://www.phac-aspc.gc.ca/std-mts/sti-its/cgst-ldcits/index-eng.php

DIFFERENTIAL DIAGNOSIS

- DISCRETE LOCALIZED CUTANEOUS INFECTIONS — superficial (impetigo, folliculitis, furunculosis), deep (carbuncles, subcutaneous abscesses)

- SPREADING DIFFUSE CUTANEOUS INFECTIONS (involves deeper dermis and subcutaneous tissues) — erysipelas, cellulitis

- DEEP SOFT TISSUE INFECTIONS — necrotizing fasciitis (polymicrobial, *S. pyogenes*), gas gangrene (*C. perfringens*)

PATHOPHYSIOLOGY

- RISK FACTORS FOR CELLULITIS

  - COMPROMISED SKIN — trauma, IDU, psoriasis, eczema, fungal disease (especially tinea pedis)

  - COMPROMISED SENSORY/PROPRIOCEPTIVE NERVES — diabetic neuropathy

  - COMPROMISED BLOOD/LYMPHATIC VESSELS — diabetes, malignancy, lymphatic or venous insufficiency; venectomy, radiation, prior cellulitis

- CELLULITIS — acute spreading infection involving the dermis and subcutaneous tissue, mostly
caused by Staphylococci and group A Streptococcus. It usually presents as a swollen, erythematous plaque with ill-defined border

**ERYSIPelas** — superficial cellulitis involving the upper dermis and lymphatics, mostly caused by group A Streptococcus. It usually presents as a raised, erythematous plaque with well-demarcated border. It occurs more commonly in infants and elderly

**Risk Factors for Skin and Soft Tissue Infections Due to MRSA/CA-MRSA** — previous MRSA infection, hospitalization, or household contacts of known MRSA; street involved/shelters/incarceration, injection drug use, athletes, children/day care

**Common Pathogens Causing Cellulitis**
- **Most Common** — *S. pyogenes* (β-hemolytic group A Streptococcus), *S. aureus*, other β-hemolytic streptococci (B, C, G, and F)
- **Surgical Wound** — *S. aureus*, *S. pyogenes*
- **Human Bite** — oral anaerobes, *Eikenella corrodens*
- **Animal Bite** — *Pasteurella multocida*, *Capnocytophaga canimorsus*
- **Tick Bite** — *Borrelia burgdorferi*, Tularemia
- **Freshwater** — *Aeromonas hydrophila*
- **Seawater** — *Vibrio vulnificus*
- **Fish Exposure** — *Erysipelothrix rhusiopathiae*, *Streptococcus iniae*
- **Hot Tub** — *Pseudomonas aeruginosa* folliculitis

**Rational Clinical Examination Series: Does This Patient Have an Infection of a Chronic Wound?**

|                          | LR+    | LR–    |
|--------------------------|--------|--------|
| Increasing pain          | 11–20  | 0.64–0.88 |
| Foul odour               | 1.5–3.1| 0.73–0.92 |
| Discouloured granulation | 1.4–1.9| 0.64–0.85 |
| Erythema                 | 1.4–1.7| 0.66–0.88 |
| Edema                    | 0.87–2.3| 0.51–1.0 |
| Heat                     | 0.80–1.1| 0.98–1.0 |
| Serous exudate           | 1.1–1.9| 0.57–0.62 |
| Purulent exudate         | 0.50–0.74| 1.1–1.3 |
| Delayed healing          | 1.0–2.3| 0.29–0.96 |
| IDSA criteria (purulent exudate or ≥2 of pain, erythema, heat, or edema) | 0.96 | 1.0 |

**Pathophysiology (Cont’d)**

**Management**

- **Treat Underlying Cause** — incision and drainage of abscesses. Elevation of affected area if possible, compression and skin hydration.
- **Antibiotics for Mild Cellulitis**
  - **Cephalexin** 500 mg PO QID, **dicloxacillin** 500 mg PO QID, or **clindamycin** 150–300 mg PO QID × 5–14 days)
- **For Systemic Toxicity or Severe Cellulitis**
  - **Cefazolin** 1–2 g IV q8h, **ceftriaxone** 1 g IV q24h, **nafcillin** 1–2 g IV q4–6 h × 7–14 days)
  - **For MRSA Associated Skin Infections**
    - **Vancomycin** 1–2 g IV q12h, **trimethoprim/sulfamethoxazole** 1 DS tab PO BID, **daptomycin** 100 mg PO QID, **tigecycline** 100 mg loading dose, then 50 mg IV q12h, **doxycycline** 100 mg PO BID, **linezolid** 600 mg PO/IV q12h.
- **For Mild Erysipelas**
  - **Ceftriaxone** 1 g IV Q4h or **cefazolin** 1–2 g IV q8h × 5–14 days

**Investigations**

- **Basic**
  - **LABS** — CBCD, lytes, urea, Cr, lactate (if suspicion of necrotizing fasciitis)
  - **Microbiology** — swab of portal of entry or any open draining wound for Gram stain and C&S, blood C&S (indicated only if systemic symptoms)

**Specific Entities**

- **Necrotizing Fasciitis**
  - **Types**
    - **Type 1** (polymicrobial infections including Enterococci, *E. coli*, non-group A *Streptococcus*, *Klebsiella*, anaerobes. Mixed infections occurring postoperatively or in those with diabetes or peripheral vascular disease, e.g. Fournier’s gangrene of perineum in diabetics), **Type 2** (monomicrobial *Streptococcus pyogenes* “Group A strep”; rarely, CA-MRSA. May occur at any age and in healthy hosts following minor trauma, penetrating injury, laceration, varicella, IDU, or childbirth)
Osteomyelitis

CAUSES

HEMATOGENOUS (monomicrobial)—S. aureus, coagulase-negative staphylococci, Gram-negative bacilli (P. aeruginosa, Serratia, E. coli), TB, fungi

CONTIGUOUS SPREAD FROM SOFT TISSUE OR JOINTS (polymicrobial)—S. aureus, coagulase-negative Staphylococci, S. pyogenes, Enterococcus, Gram-negative bacilli, anaerobes

CONTIGUOUS SPREAD WITH GENERALIZED VASCULAR INSUFFICIENCY (polymicrobial)—S. aureus, Streptococcus, Enterococcus, Proteus mirabilis, P. aeruginosa, anaerobes

DIRECT INOCULATION THROUGH TRAUMA OR SURGERY (monomicrobial or polymicrobial)—may involve skin or environmental commensal organisms

PATHOPHYSIOLOGY (CONT’D)

• LOCAL—vascular compromise (arterial insufficiency, neuropathy venous stasis), orthopedic surgery

CLINICAL FEATURES

DIABETIC FOOT ULCER—either probing of bone or ulcer area above 2 cm² is associated with ~90% chance of having underlying osteomyelitis (sens 66%, spc 85%, PPV 89%, NPV 56%). Further noninvasive testing is unlikely to improve accuracy of diagnosis

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH DIABETES HAVE OSTEOMYELITIS OF THE LOWER EXTREMITY?

Wagner grading scale

0—no open lesions; may have evidence of healed lesions or deformities
1—superficial ulcer
2—deeper ulcer to tendon, bone, or joint capsule
3—deeper tissues involved, with abscess, osteomyelitis, or tendinitis
4—localized gangrene of toe or forefoot
5—gangrene of foot (partial or total)

Clinical gestalt

Clinical judgment  9.2  0.70
Wagner grade >2  5.5  0.54

PATHOPHYSIOLOGY

ROUTE OF INFECTION

• HEMATOGENOUS—mainly central (vertebrae, sternoclavicular, sacroiliac) and sometimes long bones (femur, tibia, humerus)

• CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS—trauma, surgery, orthopedic prosthesis, decubitus ulcer

• CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS WITH GENERALIZED VASCULAR INSUFFICIENCY—ischemic ulcers, diabetic ulcers

RISK FACTORS FOR OSTEOMYELITIS

• SYSTEMIC—diabetes, sickle cell disease (Salmonella)

SPECIFIC ENTITIES (CONT’D)

• PATHOPHYSIOLOGY (type 1)—inoculation of ischemic or devitalized tissue → host immune system and antibiotics relatively ineffective → rapid spreading of infection to surrounding tissue → late signs include fever, crepitus, shock → complications include compartment syndrome, acute renal failure, sepsis. May be limb or life-threatening. May develop over a few hours

• ASSOCIATIONS—host (age >50, cancer, alcoholism, immunocompromised, malnutrition, obesity), compromised skin (burns, trauma, postoperative infection), compromised blood vessels (peripheral vascular disease, diabetes)

• CLINICAL FEATURES—typically happens over body areas with limited fibrous tissue (trunk, extremities). Pain disproportionate to physical findings. Gangrenous skin changes, bullae, tense edema, and crepitus may be seen as late signs

• DIAGNOSIS—high index of suspicion (pain >> physical findings). Plain X-ray to check for gas with type 1 necrotizing fasciitis. CT or MRI maybe useful. Early deep incisional biopsy is gold standard

• TREATMENTS—urgent surgical debridement of all necrotic tissue. Consider IVIG if significant hypotension in Group A Streptococcus necrotizing fasciitis. Polymicrobial piperacillin–tazobactam 4.5 g IV q8h plus vancomycin 1 g IV q12h, Streptococcus (penicillin G 4 MU IV q4h plus clindamycin 600–900 mg IV q8h)

PATHOPHYSIOLOGY (CONT’D)

ROUTE OF INFECTION

• HEMATOGENOUS—mainly central (vertebrae, sternoclavicular, sacroiliac) and sometimes long bones (femur, tibia, humerus)

• CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS—trauma, surgery, orthopedic prosthesis, decubitus ulcer

• CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS WITH GENERALIZED VASCULAR INSUFFICIENCY—ischemic ulcers, diabetic ulcers

RISK FACTORS FOR OSTEOMYELITIS

• SYSTEMIC—diabetes, sickle cell disease (Salmonella)
### CLINICAL FEATURES (CONT’D)

| Physical                          | LR+  | LR−  |
|----------------------------------|------|------|
| Bone exposure                    | 9.2  | 0.70 |
| Positive probe to bone finding   | 6.4  | 0.39 |
| Ulcer area >2 cm²                | 7.2  | 0.48 |
| Ulcer inflammation               | 1.5  | 0.84 |

| Laboratory                       |      |      |
|----------------------------------|------|------|
| ESR ≥ 70 mm/h                    | 11   | 0.34 |
| Swab culture                     | 1    | 1    |
| Abnormal plain radiograph        | 2.3  | 0.63 |
| Abnormal MRI                     | 3.8  | 0.14 |

**APPROACH**—“an ulcer area >2 cm², a positive probe-to-bone test result, an ESR ≥70 mm/h, and an abnormal plain radiograph are helpful in diagnosing the presence of lower extremity osteomyelitis in patients with diabetes. A negative MRI result makes the diagnosis much less likely when all of these findings are absent. No single historical feature or physical examination reliably excludes osteomyelitis. The diagnostic utility of a combination of findings is unknown. The gold standard for diagnosis is bone biopsy”

**JAMA 2008 299:7**

### INVESTIGATIONS (CONT’D)

**vertebral osteomyelitis (CT-guided biopsy can provide microbiological diagnosis to guide therapy)**
- **ANKLE BRACHIAL INDEX**—ischemic ulcers suspected

### DIAGNOSTIC ISSUES

**PLAIN FILMS**—soft tissue swelling and gas, cortical destruction, peristomal new bone formation, foreign bodies, deformities, fractures, and soft tissue gas. Usually the first imaging to investigate for osteomyelitis. However, may not detect changes until after 2–3 weeks of infection. May help make diagnosis of osteomyelitis but never excludes it (sens 61%, spc 72%, PPV 80% for diabetic foot osteomyelitis)

**BONE SCAN**—more sensitive but less specific than plain films (sens 70–100%, spc 36% for diabetic foot osteomyelitis). Useful for ruling out osteomyelitis, but cannot make the diagnosis

**INDIUM-LABELED LEUKOCYTE SCAN**—better sensitivity and specificity (but still poor) than bone scans in diabetic foot. Since WBC accumulates in the marrow, the scan is less sensitive in areas with red marrow (vertebrae, pelvis). Excellent for fracture nonunion osteomyelitis (sens 91%, spc 97%)

**MRI**—provides great anatomic details, more sensitive and specific than bone scan. Imaging of choice for specific body sites (vertebrae, diabetic foot)

**ULTRASOUND**—fluid collection adjacent to the bone without intervening soft tissue, elevation of the periosteum by >2 mm, and thickening of the periosteum. Sensitivity and specificity uncertain

**BONE BIOPSY**—gold standard for osteomyelitis and generally required in vertebral osteomyelitis. Positive blood cultures and corresponding radiologic findings may support diagnosis and sometimes replace bone biopsy. Consider holding off antibiotic therapy if not life-threatening infection to facilitate identification of organisms. Organisms from superficial skin swabs have little correlation with the actual organisms growing inside the bone, except for S. aureus

### INVESTIGATIONS

**BASIC**
- **LABS**—CBCD, ESR (monitor disease progress if elevated), urinalysis
- **MICROBIOLOGY**—blood C&S, urine C&S
- **IMAGING**—plain films (specific but insensitive), three-phase bone scan (sensitive), CT, MRI (most sensitive and specific, particularly spine and diabetic foot), indium-labeled WBC scan (specific), US, bone marrow scan, dual tracer scan

**SPECIAL**
- **ULCER PROBING**
- **BONE BIOPSY**—C&S, AFB, TB culture, fungal culture, histology; generally required

### RELATED TOPIC

Diabetes Mellitus (p. 381)
MANAGEMENT

HEMATOGENOUS—for vertebral osteomyelitis, need blood and bone cultures, then start empiric antibiotics with cloxacillin 2 g IV q4–6 h or cefazolin 2 g IV q8h. Consider vancomycin 15 mg/kg IV q12h if high local MRSA rates. Once organism identified, treat with specific antibiotic (total 6–12 weeks of antibiotics guided by susceptibility from time of biopsy or definitive surgery, with at least 2 weeks of IV therapy). If failed therapy, consider bone/soft tissue debridement and another 4–6 weeks of antibiotics after definitive surgery

CONTIGUOUS SPREAD WITHOUT VASCULAR INSUFFICIENCY—after orthopedic surgery and specimen collection, start vancomycin 15 mg/kg IV q12h. For sternal osteomyelitis, give vancomycin 15 mg/kg IV q12h, then switch to specific antibiotics (total 6 weeks of antibiotics from time of definitive surgery, usually intravenous for the duration)

CONTIGUOUS SPREAD WITH VASCULAR INSUFFICIENCY—polymicrobial. Base therapy on bone culture, empirical coverage should include anaerobes (e.g. carbapenems, piperacillin–tazobactam)

SPECIFIC ENTITIES

VERTEBRAL OSTEOMYELITIS

PATHOPHYSIOLOGY—usually results from disc-space seeding through hematogenous dissemination, seeding from urinary tract, trauma, extension of infection from adjacent structures, or as a complication of spine and disc surgery.

TREATMENTS—cloxacillin 2 g IV q4–6 h or cefazolin 2 g IV q8h. Consider vancomycin 15 mg/kg IV q12h if high local MRSA rates

PROSTHETIC JOINT INFECTIONS

PATHOPHYSIOLOGY—most commonly due to coagulase-negative staphylococci

TREATMENTS—debridement with retention of prosthesis may be possible with early-onset infection (within 3 months of surgery), short duration of symptoms (<3 weeks) with no sinus tract, a stable implant and a causative organism susceptible to quinolones (or trimethoprim–sulfamethoxazole) and rifampin, which are given for 3 months (hips) to 6 months (knees) after an initial course of appropriate IV antibiotic therapy for at least 2 weeks. If debridement and retention are not appropriate, removal of the infected prosthesis with one-stage or two-stage exchange; IV antibiotic therapy is also provided for 6 weeks following the initial surgery

NEJM 2009 361:8

Septic Arthritis

See SEPTIC ARTHRITIS (p. 309)

Tuberculosis: Pulmonary

PATHOPHYSIOLOGY

ORGANISMS—genus Mycobacterium consists of >50 species. TB is caused by M. tuberculosis complex including M. tuberculosis, M. bovis, and others. The cell envelope contains mycolic acid → resists destaining by acid alcohol, thus termed acid fast bacilli

TRANSMISSION—TB transmission is almost exclusively airborne through inhalation of minute droplet nuclei. Therefore, lungs are the primary

PATHOPHYSIOLOGY (CONT’D)

focus. However, any organs can become infected during the bacteremia that follows initial lung infection

LATENT TB INFECTION (LTBI)—follows initial infection; asymptomatic; detected by tuberculin skin test (TST) or interferon-gamma release assay (IGRA). Risk of active infection generally is 5% in the first 2 years with 5% risk of reactivation thereafter
FACTORS THAT INCREASE THE RISK OF INFECTION—1/3 of the world’s population is infected with TB. Birth in endemic area (less commonly travel) is the major risk factor; other risk factors include aboriginal populations and racial/ethnic minorities, household/institutional contacts and crowding (healthcare workers, long-term care, correctional facilities, substance abuse, and shelters).

FACTORS INCREASING THE RISK OF REACTIVATION OF LTBI—HIV infection (most important risk factor, always test those with active TB for HIV), fibronodular disease on CXR, chronic renal failure, increasing age, malignancy, transplant/immunosuppression, silicosis, chronic steroid use, TNF-α inhibitors, alcohol abuse, malnutrition, liver or kidney disease, poorly controlled diabetes, smoking, gastrectomy, jejunooileal bypass.

CLINICAL FEATURES

PRIMARY TB
- **SYMPTOMS**—fever, night sweats, pleuritic chest pain, chronic cough, anorexia, weight loss, fatigue, erythema nodosum
- **SIGNS**—often none. Primary TB usually involves the mediastinal lymph nodes (Ghon complex); hilar lymphadenopathy in the presence of RML collapse is the most common radiologic finding (2/3) with pleural effusion in 1/3. Lung infiltrates may be seen and involve lower lungs or middle lung fields most commonly with possible cavitation in areas of consolidation.

REACTIVATION TB (active pulmonary)
- **SYMPTOMS**—subacute progressive cough, yellow-green sputum (increases over time), hemoptysis (25%), chest pain/dyspnea (33%), fever/night sweats (50%), fatigue (50–66%), weight loss
- **SIGNS**—reactivation TB usually involves the apical-posterior segments of upper lobes (80–90%), cavitation (19–40%), hilar lymphadenopathy (more likely than cavitation in AIDS patients)
- **ELDERLY WITH REACTIVATION TB**—presents with fever, night sweats, or hemoptysis less often. Lesions less often cavitary and less often TST positive.

COMPLICATIONS OF PULMONARY TB—hemoptysis (rarely massive), pneumothorax (more common in endemic countries), bronchiectasis, and pulmonary destruction (rare).

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, albumin, urinalysis
- **MICROBIOLOGY**—blood C&S with mycobacterial culture, sputum Gram stain/AFB/C&S, urine AFB/C&S, HIV serology
- **IMAGING**—CXR, CT chest

SPECIAL
- **SKIN TEST**—see Diagnostic Issues for details
- **INTERFERON GAMMA RELEASE ASSAYS**—Quantiferon-TB Gold In-Tube (QFT-GIT) assay and T-SPOT TB assay
- **PCR**
- **MOLECULAR FINGERPRINTING**—tracing outbreaks
- **SUSCEPTIBILITY TESTING**—1 extra week
- **THORACENTESIS**—if effusion. Send for fluid AFB and TB culture
- **PLEURAL BIOPSY**
- **CSF**—AFB, TB culture

DIAGNOSTIC ISSUES

TUBERCULIN SKIN TEST (TST)—gold standard for diagnosing latent tuberculosis (epidemiologic tool), but not sensitive or specific to include or exclude active pulmonary TB. Given as 5 units TST-S (purified protein derivative) intradermally, measure extent of induration after 48–72 h. Skin test reaction cutoffs and corresponding population groups when test considered positive (in North America) are as follows:
- **0–4 MM**—in general, considered negative; no treatment indicated unless child <5 years of age and high risk of TB infection
- **≥5 MM**—HIV positive, recent infectious TB contact within 2 years, CXR signs (fibronodular disease), immunosuppression (TNFα inhibitors, organ transplantation, glucocorticoid treatment equivalent of ≥15 mg/day prednisone × ≥1 month), end stage renal disease
- **≥10 MM**—all others, including TST conversion within 2 years, diabetes, malnutrition (<90% ideal body weight), cigarette smoking, daily alcohol consumption >3 drinks/day, silicosis, hematologic malignancies (leukemia/lymphoma) and certain carcinomas (e.g. head and neck, lung)

Canadian Tuberculosis Standards, 7th Edition 2013

INTERFERON GAMMA RELEASE ASSAYS—sens >95%; not affected by prior BCG vaccination. Most useful for evaluation of latent TB in those with positive TST and previously vaccinated with BCG.

Related Topic
Tuberculosis in Pregnancy (p. 473)
DIAGNOSTIC ISSUES (CONT’D)

SPUTUM SMEAR
- **UTILITY**—morning sputum × 3 days (AFB, TB culture), induced sputum if necessary, bronchoscopic lavage if cannot obtain sputum. Three consecutive AFB-negative sputum samples support that patient is non-infectious and can come off isolation
- **LIMITATIONS**—smear only detects 50% of culture positive TB, and in non-endemic areas positive smear may represent non-TB mycobacterium
- **STAINING AGENTS**—standard is Ziehl–Neelsen (acid fast stain); Auramine–Rhodamine or Auramine O fluorescence staining improves sensitivity but must be confirmed with acid fast

SPUTUM CULTURE—2–8 weeks in egg media, 4–14 days if radiometric (sens 80–85%, spc 98–99%)

POLYMERASE CHAIN REACTION (PCR)—more useful in non-endemic countries to rule out other common mycobacteria. High specificity but variable sensitivity (if AFB positive, sens 94–96%, spc 99.7–100%. If AFB positive, sens 9–100%, spc 25–100%)

MANAGEMENT (CONT’D)

three times weekly for 24 weeks, or isoniazid, rifampin, pyrazinamide, plus ethambutol for 2 weeks, then twice weekly for 6 weeks, followed by isoniazid and rifampin twice weekly for 16 weeks (see guidelines for exceptions and alternate regimens when faced with resistance or drug intolerance)

TREATMENT ISSUES

VACCINATION WITH BCG (Bacillus Calmette-Guerin)—decreases miliary and meningeal TB by 75–86% and pulmonary TB by 50% in children. However, BCG leads to false-positive skin test, which may compromise contact tracing and decision to treat latent TB infection. Not routinely performed in areas with low endemic TB risk

DIRECTLY OBSERVED TREATMENT—most effective method to prevent multi-drug-resistant tuberculosis according to the WHO

MEDICATION DETAILS
- **RIFAMPIN** *(RIF)—bactericidal. Side effects include hepatic toxicity (less than INH, but induces hepatic microsomal enzymes →↑ clearance and ↓ effects of many drugs), flu-like symptoms, red-orange urine, sweat, tears*
- **ISONIAZID** *(INH)—bactericidal and inexpensive. Side effects include hepatitis (↑ with increased age and alcohol use), peripheral neuropathy (↓ with pyridoxine 10 mg PO daily or 25 mg PO daily if HIV, diabetes, malnourished, renal failure, pregnancy, or breast feeding)*
- **PYRAZINAMIDE** *(PZA)—bactericidal at acidic pH in cells. Side effects include GI intolerance, hepatic injury, hyperuricemia due to ↓ renal excretion, arthralgias*
- **ETHAMBUTOL**—mostly bacteriostatic. Main side effect is optic neuritis

DRUG MONITORING
- **BASELINE**—platelet, Cr, AST, ALP, bilirubin, uric acid (pyrazinamide), visual acuity, and red-green color discrimination (ethambutol)
- **FOLLOW-UP**—symptoms of hepatotoxicity and visual disturbance

TREATMENT OF CO-INFECTION WITH TB AND HIV—similar treatment outcome with or without HIV, but treatment of active TB infection in HIV patients should be extended beyond 6 months if bacteriologic or clinical response is slow or suboptimal. Also beware of TB and HIV drug interactions (protease inhibitors and nucleoside reverse transcriptase inhibitors may cause toxic levels of rifampin, which should be replaced by rifabutin)
## Approach to Gram Stain, Culture, and Sensitivity

### Gram-Positive Cocci

**Clusters** (catalase positive) (Staphylococci)  
- **Coagulase Positive** — *S. aureus*  
- **Coagulase Negative** — *S. epidermidis*, *S. saprophyticus*, *S. hominis*, *S. lugdunensis*, *S. schleiferi*

**Pairs/Chains** (catalase negative)  
- **α-Hemolytic Streptococci** — *S. pneumoniae*, viridans group streptococci
- **β-Hemolytic Streptococci** — *S. pyogenes* (Group A strep), *S. agalactiae* (Group B strep), group C, F, G strep
- **Enterococcus** — *E. faecalis*, *E. faecium*
- **Others** — *Abiotrophia*, *Granulicatella* (nutrient variant Strep), *Leuconostoc*, *Lactococcus*, *Aerococcus*

### Gram-Positive Bacilli

**Acid Fast** (mycobacterium) — *M. tuberculosis*, *M. leprae*, *M. avium-intracellulare* complex, or non-tuberculous Mycobacteria (NTM, also known as mycobacteria other than TB [MOTT]). These organisms have Gram-positive-type cell walls, but do not stain Gram positive due to the waxy mycolic acids in the cell envelope.

**Anaerobic** — *Peptostreptococcus*, *Streptococcus*, *Anaerococcus*

### Gram-Negative Cocci

**Neisseria** — *N. meningitidis* (diplococci), *N. gonorrhoeae* (diplococci), other Neisseria

**Moraxella** — *M. catarrhalis*

### Gram-Negative Bacilli

**Aerobic**  
- **Glucose Fermenting and Lactose Fermenting** — a number of Enterobacteriaceae including *E. coli*, *Citrobacter*, *Enterobacter*, *Klebsiella*, *Serratia*
- **Glucose Fermenting but Non-Lactose Fermenting** — *Shigella*, *Salmonella*, *Yersinia*, *Edwardsiella*, *Vibrio* (oxidase positive), *Aeromonas* (oxidase positive), *Plesiomonas* (oxidase positive)
- **Non-Glucose and Non-Lactose Fermenting**  
  - **Oxidase Positive** — *Pseudomonas*, *Ralstonia*, *Burkholderia*, *Roseomonas*, *Sphingomonas*
  - **Oxidase Negative** — *Stenotrophomonas*, *Acinetobacter*, *Chryseomonas*

**Anaerobic** — *Bacteroides fragilis*, *Fusobacterium*, *Prevotella*, *Porphyromonas*

**Others** — *Eikenella* (*cats*), *Pasteurella* (*dogs*), *Capnocytophaga* (dogs), *Kingella*, *Actinobacillus*, *Cardiobacterium*, *Hyphomicrobium*, *Capnocytophaga* (dogs), *Kingella*, *Actinobacillus*, *Cardiobacterium*, *Hyphomicrobium*, *Capnocytophaga* (dogs), *Kingella*, *Actinobacillus*, *Cardiobacterium*, *Hyphomicrobium*

**Specific Organisms**

**Non-Gram-Stainable** — *Chlamydia*, *Mycoplasma*, *Ureaplasma*, *Trichomonas*, *Treponema*, *Coxiella*, *Ehrlichia*, *Mycobacteria*

**Antibiotic Susceptibility and Resistance**

**Group A Streptococcal Infections** — resistant to clindamycin

**Streptococcus Pneumoniae** — may develop resistance to penicillin by altered penicillin-binding protein
S. AUREUS (MSSA)—may develop resistance to penicillin by β-lactamase

PSEUDOMONAS—various intrinsic mechanisms conferring resistance. Need to treat with dual antibiotic therapy for serious infections if therapy for >2 weeks or if susceptibility not yet available

VRE—vancomycin-resistant enterococci

MRSA—S. aureus that is resistant not only to penicillin, but also penicillinase-resistant penicillins (methicillin, nafcillin, oxacillin). In general, hospital MRSA strains have broader resistance (e.g. clindamycin, trimethoprim–sulfamethoxazole, tetracyclines) than community-associated MRSA strains (CA-MRSA). Risk factors for hospital MRSA infections include frequent hospital visits and contact with MRSA-infected individuals; CA-MRSA is associated with crowding, acute and chronic skin disease, poor hygiene, sharing of contaminated items, contact sports, and IDU

β-LACTAMASE-RESISTANT BACTERIA—

constitutive (E. coli*, Klebsiella*, Haemophilus, Neisseria, bacteroides), inducible (S. aureus, Serratia†*, Providencia†, Pseudomonas, Indole-positive Proteus*, Citrobacter†*, Enterobacter†*, Hafnia†*, Acinetobacter†*, Morganella†*)

†★SPICE-HAM★ organisms with inducible, chromosomally mediated cephalosporinases (AmpC type β-lactamases) resistant to penicillins, first and second generation cephalosporins, cephamycins, and β-lactamase inhibitors

*These organisms may have extended spectrum β-lactamase (ESBL) resistant to all β-lactams except carbapenems

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE (CONT’D)

GENTAMICIN AND TOBRAMYCIN DOSING

TOXICITY—nephrotoxicity, ototoxicity, neuromuscular blockade (rare). Serum aminoglycoside levels correlate with nephrotoxicity

LOADING DOSE (TRADITIONAL DOSING: Q8H)—dependent on indication. For mild infection, uncomplicated UTI, synergy with β-lactams for Gram positive infections, give 0.6–1.2 mg/kg IV q8h. For serious Gram-positive infection or sepsis, give 2.5 mg/kg IV. For life-threatening infections, give 3.0 mg/kg IV

MAINTENANCE DOSE (TRADITIONAL DOSING: Q8H)

- START—1.7 mg/kg IV q8h. Monitor serum levels after steady state reached; i.e. 3–5 half-lives (after third dose). Monitor renal function and ototoxicity every 3 days

- PEAK LEVELS—obtain 30–45 min after end of infusion. Should be 4.2–8.4 μmol/L [2–4 μg/mL] when drug is being given for synergy or uncomplicated infections, 12.6–16.8 μmol/L [6–8 μg/mL] for serious Gram-negative infection or sepsis, and 14.7–18.9 μmol/L [7–9 μg/mL] for life-threatening infections

- TROUGH LEVELS—obtain 0–30 min prior to scheduled dose. Should be <4.2 μmol/L [<2 μg/mL] to prevent toxicity

- ADJUSTMENTS—dosing interval is dependent on renal function (CrCl >60 mL/min, q8h; 40–60 mL/min, q12h; 20–40 mL/min, q24h; <20 mL/min single dose then measure serum concentration and give PRN). Changes in dose without changes in interval will result in proportional changes in both peak and trough serum drug concentrations. Prolongation of dosing interval will also reduce both, but particularly trough level
| Antibiotics               | Mechanism                                      | Gram positive | Gram negative | Anaerobes | Others | Renal adjustments |
|--------------------------|------------------------------------------------|---------------|---------------|-----------|--------|-------------------|
| **Penicillins**          | **Bactericidal, cell wall synthesis**          | ++ Strep      | ++            | ++        | Syphilis | Yes (dose + interval) |
| Penicillin G 2–4 M units IV q4–6 h | **++ Strep inhibition and lysis** |               |               |           |         |                   |
| Penicillin V 250–500 mg PO TID/ QID | ++ Strep |               |               | ++        |         | Yes (dose + interval) |
| Cloxacillin/nafcillin/oxacillin 1–2 g IV q4–6 h | ++S. aureus |               |               |           | No      |                   |
| **Amino-Penicillins**    | **Bactericidal, cell wall synthesis**          | +++ Strep/Entero | +/−H. flu, +/−E col | Listeria |         | Yes (interval) |
| Ampicillin 1–2 g IV q4–6 h | **+++Strep/Entero inhibition and lysis**      |               |               |           |         |                   |
| Amoxicillin 250–1,000 mg PO TID | +++Strep/Entero |               |               | +/−H. flu, +/−E col |         | Yes (interval) |
| Amox/clavulanate 875/125 mg PO BID | +++Strep/Entero |               |               | ++H. flu, E col | +++     | Yes (interval) |
| **Anti-pseudomonal Penicillins** | **Bactericidal, cell wall synthesis**          | ++            | ++Pseudo      | ++        |         | Yes (dose + interval) |
| Piperacillin 3–4 g IV q4–6 h | **++Staph** |               |               | ++Pseudo/H. flu | +++     | Yes (dose + interval) |
| Pip/tazo 3.375 g q6h–4.5 g IV q8h | ++Staph |               |               | ++Pseudo/H. flu | +++     | Yes (dose + interval) |
| Ticarcillin 3–4 g IV q4–6 h | ++            |               |               | ++Pseudo   |         | Yes (dose + interval) |
| Ticarcillin/clavulanate 3.1 g IV q4–6 h | ++     |               |               | ++Pseudo   |         | Yes (dose + interval) |
| **Monobactam and Carbapenems** | **Bactericidal, cell wall synthesis**          | +++Pseudo     | +++           | +++       |         | Yes (dose) |
| Aztreonam 1–2 g IV q6–8 h  | **+++Pseudo inhibition and lysis**            |               |               | +++       |         |                   |
| Imipenem 500 mg IV q6h   | +++            |               |               | +++Pseudo |         | Yes (dose + interval) |
| Meropenem 1 g IV q8h     | ++            |               |               | +++Pseudo |         | Yes (dose + interval) |
| Ertapenem 1 g IV q24h    | ++            |               |               | +++(no Pseudo) | +++   | Yes (dose) |
| Doripenem 500 mg IV q8h  | ++            |               |               | +++       |         | Yes (dose + interval) |
| **First-Generation Cephalosporins** | **Bactericidal, cell wall synthesis**          | +++           | +            | +++       |         | Yes (interval) |
| Cefazolin 1–2 g IV q8h   | **+++Pseudo inhibition and lysis**            |               |               | ++        |         |                   |
### Antibiotics and their Mechanism

| Antibiotics                  | Mechanism                                      | Gram positive | Gram negative | Anaerobes | Others | Renal adjustments |
|------------------------------|------------------------------------------------|---------------|---------------|-----------|--------|-------------------|
| Cephalexin 250–1000 mg PO QID| +++++                                          | +             |               |           |        | Yes (interval)    |
| **Second-Generation Cephalosporins** |                                             |               |               |           |        |                   |
| Cefuroxime 750–1500 mg IV q8h| Bactericidal, cell wall synthesis inhibition and lysis | ++            | ++            |           |        | Yes (interval)    |
| Cefuroxime 125–500 mg PO BID| ++                                             | ++            |               |           |        | Yes (interval)    |
| Cefprozil 250–500 mg PO q12h| ++                                             | ++            |               |           |        | Yes (interval)    |
| Cefaclor 250–500 mg PO BID  | ++                                             | ++            |               |           |        | Yes (interval)    |
| **Third/Fourth Generation Cephal.** |                                             |               |               |           |        |                   |
| Cefoxitin 1–2 g IV q6–8 h   | Bactericidal, cell wall synthesis inhibition and lysis | +++           | +++           | ++        |        | Yes (interval)    |
| Cefotaxime 1–2 g IV q6–8 h   | +++                                            | +++           |               |           |        | Yes (interval)    |
| Ceftriaxone 1–2 g IV q24h    | +++                                            | +++           |               |           |        | No                |
| Ceftazidime 1 g IV q8–12 h   | +++                                            | +++Pseudo     |               |           |        | Yes (interval)    |
| Cefepime 1–2 g IV q12h       | +                                              | +++Pseudo     |               |           |        | Yes (interval)    |
| Cefixime 400 mg PO daily     | +                                              | ++            |               |           |        | Yes (interval)    |
| Ceftaroline 600 mg IV q8–12 h| +++MRSA                                        | ++            |               |           |        | Yes (interval)    |
| **Aminoglycosides**         |                                                |               |               |           |        |                   |
| Gentamicin 5–7 mg/kg IV q24h| Bactericidal, binds to 30S and 50S ribosomes    | Entero (syn)  | +             | Pseudo    |        | Yes (dose + interval) |
| Tobramycin 5–7 mg/kg IV q24h| +/-Entero (syn)                                 | ++            | Pseudo        |           |        | Yes (dose + interval) |
| Amikacin 7.5 mg/kg q12h      | +/-Entero (syn)                                 | ++            | Pseudo        |           |        | Yes (dose + interval) |
| Streptomycin 15 mg/kg IM or IV q24h | Entero (syn)                                   | ++            | Pseudo        | AFB, Plague |        |                   |
| **Fluoroquinolones**        |                                                |               |               |           |        |                   |
| Ciprofloxacin 500 mg PO/400 mg IV BID | Bactericidal, inhibit DNA synthesis through inhibition of DNA gyrase and topoisomerase | +++Pseudo   |               | AFB       |        | Yes (interval)    |
| Norfloxacin 400 mg PO BID    | +++                                            |               |               |           |        | Yes (dose ± interval) |
| Antibiotics         | Mechanism                                           | Gram positive | Gram negative | Anaerobes | Others     | Renal adjustments     |
|---------------------|-----------------------------------------------------|---------------|---------------|-----------|------------|-----------------------|
| Ofloxacin 200–400 mg PO BID |                                                      | ++            | +++           | AFB       | Yes (dose ± interval) |
| Levofloxacin 500–750 mg PO/IV daily |                                                      | ++            | +++           | AFB       | Yes (dose ± interval) |
| Moxifloxacin 400 mg PO/IV daily |                                                      | ++            | +++           | AFB       | Yes (dose ± interval) |
| Gemifloxacin 320 mg PO daily |                                                      | ++            | +++           | AFB       | Yes (dose ± interval) |
| **Macrolides**       |                                                     |               |               |           |            |                       |
| Azithromycin 250 mg PO daily | Bacteriostatic, binds to 50S ribosomes               | +             | ++H. flu/legion| +         | Mycoplasma and Chlamydia for all macrolides | No |
| Clarithromycin 250–500 mg PO BID |                                                      | +             | ++H. flu/legion| +         | Chlamydia for Yes (dose) all macrolides | No |
| Erythromycin 250–500 mg PO q6–12 h |                                                      | +             | +Legion       | +         | Chlamydia for Yes (dose) all macrolides | No |
| **Tetracyclines**    |                                                     |               |               |           |            |                       |
| Doxycycline 100 mg PO/IV q12h | Bacteriostatic, binds to 30S ribosomes               | +             | +Chlamydia    | +         | No |
| Minocycline 50–100 mg PO daily-BID |                                                      | +             | +Chlamydia    | +         | No |
| Tetracycline 500 mg PO QID |                                                      |                   | +Chlamydia    | +         | Avoid |
| Tigecycline 100 mg IV, then 50 mg q12h | +++MRSA, VRE | +             | +Chlamydia    | +         | No |
| **Sulfa**            |                                                     |               |               |           |            |                       |
| Sulfamethoxazole/Trimethoprim 1–2 | Bactericidal, blocks DNA synthesis | +             | ++Steno, +PJP | +         | Yes (interval) |
| SS/DS tab PO BID (also available IV) |                                                      |                   |               |           |                       |
| **Clindamycin**      |                                                     |               |               |           |            |                       |
| Clindamycin 150–450 mg PO QID or 300–600 mg IV q6–12 h | Bacteriostatic, binds to tRNA complex                   | ++            | +++           | +         | No |
| **Metronidazole**    |                                                     |               |               |           |            |                       |
| Metronidazole 500 mg PO/IV q12h | Bactericidal, DNA breakage H. pylori, G. vaginalis | +              | ++C. diff     | +         | protozoa No |
|                     |                                                     |                   |               |           |                       |
| GENTAMICIN AND TOBRAMYCIN DOSING (CONT'D) |                                                      |               |               |           |            |                       |
| Approach to Gram Stain, Culture, and Sensitivity |                                                      |               |               |           |            |                       |
| Antibiotics            | Mechanism                                      | Gram positive | Gram negative | Anaerobes | Others | Renal adjustments |
|------------------------|------------------------------------------------|---------------|---------------|-----------|--------|-------------------|
| **Glycopeptides**      |                                                |               |               |           |        |                   |
| Vancomycin 15 mg/kg IV q12h | Bactericidal, interferes with peptidoglycan and RNA synthesis | +++           |               |           |        | Yes (interval)    |
|                        | S. epidermidis, MRSA, Entero                   |               |               | ++C. diff |        |                   |
| **Oxazolidinones**     |                                                |               |               |           |        |                   |
| Linezolid 600 mg PO/IV q12h | Bactericidal (Strep) and bacteriostatic (Staph, entero), binds to 50S ribosomes | ++MRSA, VRE   | +             | ++AFB    | No     |                   |
| **Streptogramins**     |                                                |               |               |           |        |                   |
| Quinupristin/dalfopristin 7.5 mg/kg IV q8h via central line | Inhibits late + early protein synthesis | ++MRSA, VRE (not E. faecalis) | +          |          | No     |                   |
| **Lipopeptides**       |                                                |               |               |           |        |                   |
| Daptomycin 4–6 mg/kg q24h | Bactericidal, disrupts cell membrane           | ++MRSA, VRE   | +             |          | Yes (interval) |
ONCE-DAILY GENTAMICIN AND TOBRAMYCIN DOSING

RATIONALE—optimize treatment of Gram-negative infections with less nephrotoxicity than q8h dosing. Similar ototoxicity and neuromuscular toxicity

NOT RECOMMENDED—monotherapy for infections outside urinary tract, pregnant patients, dialysis patients, endocarditis, CNS infections, osteomyelitis, ophthalmologic infections, surgical prophylaxis, patients with rapid drug clearance (e.g. burns >20% BSA), Gram-positive infections, patients receiving concurrent ototoxins (e.g. furosemide) neonates, pediatric patients with significant renal dysfunction, duration of therapy >14 days

LOADING DOSE—5–7 mg/kg IV

MAINTENANCE DOSE (5–7 mg/kg IV q24–48 h)
  • START—monitor serum level 6–14 h after first dose. Monitor renal function and ototoxicity q3d
  • ADJUSTMENTS—dosing interval (q24–48 h) is based on 6–14 h serum level (Hartford nomogram, Antimicrob Agents Chemother 1995 39:3). Pharmacy consult to assist with dosing (once daily dosing provides peak levels of 15–31–46 μmol/L [22 μg/mL] and trough levels <2.1 μmol/L [<1 μg/mL] to prevent toxicity. Peak and trough levels do not need to be monitored)

DOSE WEIGHT FOR AMINOGLYCOSIDES— for obese patient (i.e. actual body weight (BW) >125% of ideal body weight (IBW)), use adjusted body weight (ABW) for dose determination:
  • ABW (kg) = IBW +0.4(BW-IBW)
  Note: 1 kg = 2.2 lbs. See p. 460 for IBW calculation

VANCOMYCIN TOXICITY AND DOSING (CONT’D)

MAINTENANCE DOSE—30 mg/kg (actual body weight) per day divided into 2–4 doses (maximum usually 1.5 g/dose)
  • START—monitoring after steady state, i.e. after third dose normally, or after second dose if dosing interval >48 h. Monitor only if treatment duration >14 days in patients with stable renal function and mild/moderate infection, or treatment duration >4 days in patients with unstable renal function or severe infection
  • TROUGH LEVELS—obtained 30–60 min before next scheduled dose. Should be at least 6.9–10.4 μmol/L [10–15 μg/mL]; adjust to 10.4–13.8 μmol/L [15–20 μg/mL] for serious infections (endocarditis, osteomyelitis)
  • PEAK LEVELS—there is no correlate for efficacy or toxicity and therefore should not be monitored
  • ADJUSTMENTS—dosing interval is dependent on renal function (CrCl >100 mL/min, q12h; 80–100 mL/min, q18h; 60–80 mL/min, q24h; 40–60 mL/min, q36h; 25–40 mL/min q48h; <25 mL/min, single dose then measure serum concentration and give PRN). Changes in dose without changes in interval will result in proportional changes in both peak and trough serum drug concentrations. Prolongation of dosing interval will also reduce both, particularly trough level

PENICILLIN ALLERGY

HISTORY—characterize reaction (age when reaction occurred, timing of reaction after penicillin administration, type of reaction, route of administration, reason for penicillin, any other medications at the time, resolution), any similar antibiotics since

CROSS-REACTIVITY—incidence of cross-reactivity to cephalosporins when patient has penicillin allergy by history is <2%. Carbapenems and first/secondgeneration cephalosporins have higher cross-reactivity in the penicillin allergic than third-generation cephalosporins and aztreonam. It is often safe to use these medications, with the first dose monitored. If safety unclear, skin testing provides reassurance. For patients with a history of penicillin allergy, those with positive and negative skin test have 5.6% and 1.7% chance of developing cross-reactivity with cephalosporin, respectively

NEJM 2006 354:6
Approach to Empiric Antibiotics

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT ALLERGIC TO PENICILLIN?
HISTORY—history of penicillin allergy for predicting positive response to penicillin skin test result (LR+ 1.9, LR− 0.5), for predicting allergic response (anaphylaxis, positive skin test, or response to second course of penicillin [LR+ >11, LR− 0.98]).

TYPES OF ALLERGIC REACTIONS
★ACID★ ANTIBODY-MEDIATED (IgE), Cytotoxic (antibody-dependent), Immune-complex-mediated, Delayed hypersensitivity reaction
TYPE I—immediate <1 h, IgE antibodies mediated, anaphylaxis, hypotension, laryngeal edema, wheezing, angioedema, urticaria
TYPE II—> 72 h, IgG and complement mediated, increased clearance of RBC and platelets by lymphoreticular system
TYPE III—> 72 h, IgG and IgM immune complexes mediated, serum sickness, tissue injury
TYPE IV—> 72 h, contact dermatitis

OTHERS—> 72 h, maculopapular or morbilliform rashes

APPRAOH—“only 10–20% of patients reporting a history of penicillin allergy are truly allergic when assessed by skin testing. Taking a detailed history of a patient’s reaction to penicillin may allow clinicians to exclude true penicillin allergy, allowing these patients to receive penicillin. Patients with a concerning history of type I penicillin allergy who have a compelling need for a drug containing penicillin should undergo skin testing. Virtually all patients with a negative skin test result can take penicillin without serious sequelae”

JAMA 2001 285:19

UPDATE—patients with a negative skin test result may still react to a repeat course of penicillin (~10%) but the likelihood of a life-threatening reaction is greatly reduced. Patients with a well-documented immediate reaction to penicillin are ~90% likely to react with subsequent courses

The Rational Clinical Examination. McGraw-Hill, 2009

GENERAL APPROACH

CHOICE OF EMPIRIC ANTIBIOTIC—based on the most likely and deadly organisms for each type of infection. Thus, a good understanding of the pathophysiology of each infection and the local resistance pattern of various organisms is essential

CULTURE AND SUSCEPTIBILITY—should always be performed to facilitate targeted antibi-otic treatment except for mild infections. However, the specific organism may not be ident-ified even if multiple cultures are taken. In this case, the clinician must rely on clinical judgment and continue treatment with empiric antibiotic(s)

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT’D)
tazobactam or a carbapenem. Duration of treatment is at least 10–14 days with rationalization of antibiotics when susceptibility results available. See p. 108 for details

MENINGITIS (S. pneumoniae, N. meningitidis, Listeria, HSV)—ceftriaxone/cefotaxime ± ampicillin ± vancomycin. Add acyclovir if CSF suggests viral picture. Duration of treatment is 7–21 days. See p. 269 for details

COMMUNITY-ACQUIRED PNEUMONIA (S. pneumoniae, Klebsiella, Mycoplasma)—macrolides ± cefotaxime or respiratory fluoroquinolones. Duration of treatment is usually 7 days. See p. 7 for details

ASPIRATION PNEUMONIA (anaerobes, Staph, GNB)—levofloxacin plus metronidazole. Duration of treatment is usually at least 7 days. See p. 7 for details

ICU/VENTILATOR-ASSOCIATED PNEUMONIA (GNB, Pseudomonas)—cefepime or piperacillin–tazobactam or carbapenem. Duration of treatment is usually 8 days (p. 105)
SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT’D)

ENDOCARDITIS (S. aureus, S. viridans, Enterococcus) Duration of treatment is highly variable. See AHA guidelines and p. 60 for details
- NATIVE VALVE DISEASE—ampicillin + cloxacillin/nafcillin or vancomycin plus gentamicin
- INJECTION DRUG USE—cloxacillin or vancomycin plus gentamicin
- PROSTHETIC VALVE DISEASE—vancomycin plus gentamicin

ACUTE BLOODY DIARRHEA (Salmonella, Shigella, Campylobacter)—ciprofloxacin. Duration of treatment is 3 days. See p. 137 for details

ANTIBIOTIC-ASSOCIATED DIARRHEA (C. difficile)—oral metronidazole. Duration of treatment is 10 days. See p. 138 for details

PERITONITIS/INTRA-ABDOMINAL SEPSIS (coliforms, anaerobes)—pipericillin–tazobactam, imipenem, or ampicillin plus ciprofloxacin plus metronidazole. Treat until WBC/peritonitis resolved

FEVER IN SPLENECTOMIZED PATIENT (H. influenza, N. meningitidis, S. pneumoniae, Capnocytophaga canimorsus)—cefotaxime/ceftriaxone. Duration of treatment is usually 10–14 days. See p. 164 for further information

URINARY TRACT INFECTION (E. coli, Klebsiella, Enterococcus, Proteus, S. saprophyticus)—nitrofurantoin, trimethoprim–sulfamethoxazole, ciprofloxacin, fosfomycin. Duration of treatment is 3 days if uncomplicated UTI, otherwise 14–21 days. See p. 272 for details

CELLULITIS (Staphylococcus, Streptococcus)—cefazolin, cloxacillin, or cephalexin. Vancomycin if MRSA suspected. Duration of treatment is usually 7–10 days. See p. 275 for details

HUMAN BITE (Gram positive, Eikenella, anaerobes)—amoxicillin–clavulanate, or clindamycin plus ciprofloxacin

DIABETIC FOOT (polymicrobial)—amoxicillin–clavulanate or ciprofloxacin plus clindamycin, or trimethoprim–sulfamethoxazole plus metronidazole. Treat until resolution. May require IV antibiotics with Pseudomonas coverage (e.g. pipericillin–tazobactam; carbapenem). Osteomyelitis likely if ulcer >2 cm² or probe touches bone. See p. 277 for details

NECROTIZING FASCIITIS—surgical treatment is mandatory. For polymicrobial infection, cefotaxime plus clindamycin, pipericillin–tazobactam, or ampicillin/penicillin G plus ciprofloxacin/gen-tamicin plus metronidazole. For Streptococcus, penicillin G plus clindamycin. See p. 275 for details

OSTEOMYELITIS (Gram positive, Gram negative, anaerobes)—for Gram-positive coverage, cefazolin, or vancomycin. For Gram-negative coverage, ceftriaxone or ciprofloxacin. For Pseudomonas, piperacillin or carbapenem or ceftazidime, plus ciprofloxacin or aminoglycoside. Duration of therapy usually at least 6 weeks. See p. 277 for details

SEPTIC ARTHRITIS—vancomycin, cloxacillin, or cefazolin for Gram-positive coverage, ciprofloxacin or ceftriaxone for Gram-negative coverage. Usual duration 4 weeks. See p. 309 for details

**Hepatitis B**

See HEPATITIS B (p. 145)

**Hepatitis C**

See HEPATITIS C (p. 147)

**Herpes Simplex Virus Infection**

See HERPES SIMPLEX VIRUS (p. 416)
Human Immunodeficiency Virus

RISK FACTORS FOR HIV

SEXUAL CONTACT
PARENTERAL—IDU, transfusion, or unsafe needle use in developing world, health workers
MATERNAL–FETAL—in-utero, delivery, breast feeding

ACUTE HIV INFECTION

STRAINS—HIV1 globally; HIV2 mainly in West Africa
SYMPTOMS—acute febrile “mononucleosis-like” illness, lymphadenopathy, pharyngitis, rash and headache within 1–6 weeks post-exposure. Hematologic (lymphopenia, thrombocytopenia) and liver enzyme abnormalities
DIAGNOSIS—ELISA assay (sens ~100%, spc <100%) → if positive, repeat ELISA → if positive, Western blot → if indeterminate, repeat Western blot 4 weeks, 3 months, and 6 months later. If during window period (2 weeks post-exposure), may perform viral load testing

BASIC WORKUP FOR THE NEWLY DIAGNOSED
• HIV STATUS—viral load, CD4 count, genotypic antiretroviral drug resistance testing
• BASELINE—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, TSH, glucose, fasting lipid profile, lipase, CK, HLA B*5701 (for abacavir hypersensitivity), ßhCG, CXR, ECG, urinanalysis
• CO-EXISTING/OPPORTUNISTIC INFECTIONS—HAV serology, HBV testing (HBsAg, HBsAb, HBeAb. If HBsAg or HBeAb positive, check HBV DNA as well), HCV testing (HCV antibodies). If HCV positive, HCV RNA, assess genotype and order fibroscan. Pap smear, anal screening

CD4 COUNT AND PATHOLOGIES IN HIV PATIENTS

| CD4 count (/mm³) | >500 | 200–500 | 100–200 | <100 |
|------------------|------|---------|---------|------|
| Kaposi sarcoma    | +    | +       | +       | +    |
| Bacterial         | +    | +       | +       | +    |
| TB                | +    | +       | +       | +    |
| HSV               | +    | +       | +       | +    |
| Candida           | +    | +       | +       | +    |
| Coccidioides      | +    | +       | +       | +    |
| Histoplasma       | +    | +       | +       | +    |
| PJP               | +    | +       | +       | +    |
| Cryptococcus      | +    | +       | +       | +    |
| Toxoplasma        | +    | +       | +       | +    |
| CMV               | +    | +       | +       | +    |
| MAC               | +    | +       | +       | +    |
| CNS lymphoma      | +    | +       | +       | +    |

VIRAL LOAD—rate of progression (speed of train). Indicates activity of viral replication. Critical measure of effect of antiretroviral therapy, once started

CD4 COUNT—progress and stage of disease (distance to crash). Indicates relative health of immune system and risk of opportunistic complication

FOLLOW-UP—viral load and CD4 count (usually 3–4-month intervals, or q2–8 weeks if change of HAART)

AIDS—CD4 < 200/mm³ or any AIDS-defining diseases
• BACTERIAL—MAC, TB, recurrent Salmonella sepsis
• VIRAL—CMV retinitis, chronic HSV, PML
• FUNGAL—esophageal candidiasis, extrapulmonary coccidioidomycosis, histoplasmosis or cryptococcosis
• PARASITIC—Pneumocystis jiroveci pneumonia (PJP), toxoplasmosis, chronic Cryptosporidiosis or isosporiasis
• HIV—HIV encephalopathy, wasting syndrome
• NEOPLASMS—Kaposi’s sarcoma, CNS lymphoma, non-Hodgkin’s lymphoma, cervical carcinoma

MAJOR CAUSES OF DEATH IN HIV PATIENTS ON HAART—AIDS (30%), liver disease (14%), cardiovascular disease (9%), non-AIDS cancers (8%)
CNS LESIONS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **BRAIN ABSCESS**—toxoplasma (CD4 < 100/mm³, usually multiple ring-enhancing lesions), tuberculosis (any CD4), Cryptococcus (CD4 < 100/mm³), Histoplasma (CD4 < 500/mm³), aspergillosis

- **CNS LYMPHOMA** (CD4 < 100/mm³)

- **PROGRESSIVE MULTI-FOCAL LEUKOENCEPHALOPATHY** (PML, CD4 < 100/mm³)—reactivation of JC virus, hypodense white matter lesion

**DIAGNOSIS**—CBC, lytes, urea, Cr, blood C&S, toxoplasma IgG antibodies, EBV PCR, JC virus PCR, CT/MR head, PET scan (CNS lymphoma has higher activity than abscess), brain biopsy (if suspect CNS lymphoma). The combination of (1) multiple ring enhancing lesions, (2) positive antitoxoplasmosis antibodies, and (3) lack of toxoplasma prophylaxis in a HIV patient with CD4 count <100/mm³ has 90% PPV for diagnosing toxoplasma

**TREATMENT OF TOXOPLASMOsis**—pyrimethamine plus either sulfadiazine or clindamycin

CHRONIC MENINGITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **CRYPTOCOCCUS** (CD4 < 100/mm³)—ubiquitous fungus. High opening pressure (>200 cmH₂O)

- **BACTERIAL MENINGITIS** (any CD4)—N. meningitis, S. pneumoniae, H. influenzae

- **VIRAL MENINGITIS** (any CD4)—HSV encephalitis

**DIAGNOSIS**—CBC, lytes, urea, Cr, blood C&S, serum CRAG (sens 95% for Cryptococcus), CT head, lumbar puncture (for Cryptococcus and cryptoantigen)

**TREATMENT OF CRYPTOCOCCUS**—induction with amphotericin B 0.7 mg/kg IV daily plus flucytosine 25 mg/kg PO QID, switch to fluconazole 400 mg PO daily 2 months for consolidation, followed by fluconazole 200 mg PO daily as maintenance. Management of increased intracranial pressure may be needed (neuroimaging to rule out concomitant space-occupying lesions, repeated LP to decrease ICP)

ESOPHAGITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
  - CANDIDA (CD4 < 500/mm³)—50–70%
  - HSV (any CD4)—5–10%
  - CMV (CD4 < 100/mm³)—5–15%

- **NON–INFECTION**—GERD, pill esophagitis, neoplasms

- **IDIOPATHIC** (any CD4)—10–30%

**DIAGNOSIS**—empiric therapy (fluconazole), endoscopy with cultures for fungus, virus, and biopsy

HEPATITIS/CHOLANGITIS/PANCREATITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
  - TB (any CD4)
  - MYCOBACTERIUM AVIUM COMPLEX (MAC, CD4 < 100/mm³)—M. avium, M. intracellulare
  - VIRUSES—HBV, HCV, CMV
  - PARASITES—Cryptosporidium, Microsporidium, Cyclospora

- **ALCOHOL**

- **DRUGS**—antiretrovirals, antibiotics (sulfa, isoniazid, rifampin, ketoconazole, fluconazole)

**DIAGNOSIS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, lipase, INR, cultures and serologies, US abd, CT abd, ERCP
COLITIS/DIARRHEA IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
  - **BACTERIAL**—Salmonella, Shigella, Campylobacter, Yersinia, EHEC, EIEC, C. difficile
  - **TB** (any CD4)
  - **MYCOBACTERIUM AVIUM COMPLEX** (MAC, CD4 < 100/mm³)—M. avium, M. intracellulare
  - **CMV** (CD4 < 100/mm³)
  - **PARASITIC** ★ MAGIC ★—Microsporidium, Entamoeba, Giardia, Isospora, Cryptosporidium
- **MEDICATIONS**—antiretrovirals, antibiotics
- **AIDS ENTEROPATHY**—diagnosis of exclusion

DIAGNOSIS—CBCD, lytes, urea, Cr, stool C&S, stool O&P with acid fast staining, stool MAC, C. diff toxin, fecal WBC, Cryptosporidium, microsporidium

TREATMENT OF MAC—clarithromycin 500 mg PO BID or azithromycin 600 mg PO daily, plus ethambutol 15 mg/kg PO daily, plus rifabutin 600 mg PO daily for at least 12 months and at least 6 months of immune reconstitution (CD4 > 100–200/mm³)

AIDS-ASSOCIATED MALIGNANCIES

AIDS-DEFINING MALIGNANCIES

- **Kaposi’s sarcoma** (any CD4)—strongly associated with HHV8. Lesions may involve skin, oral mucosa, lungs, and GI tract. Treat with liposomal doxorubicin. Lesions may also resolve with antiretroviral treatment
- **NON-HODGKIN’S LYMPHOMA** (CD4 < 100/mm³)—diffuse large B-cell lymphoma, primary effusion lymphoma (associated with HHV8 and EBV), and plasmablastic lymphomas. Treat with combination chemotherapy (CHOPR)
- **PRIMARY CNS LYMPHOMA** (CD4 < 100/mm³)—strongly associated with EBV. Treat with radiation and/or high-dose methotrexate or intrathecal chemotherapy
- **CERVICAL CARCINOMA** (any CD4)—strongly associated with HPV. Treat with surgery, radiation, and/or chemotherapy (cisplatin)

NON-AIDS-DEFINING MALIGNANCIES—increased incidence of Hodgkin’s lymphoma, multiple myeloma, anogenital cancer, testicular cancer (seminoma), and basal cell carcinoma in HIV patients. Lung cancer, colorectal cancer, melanoma, squamous cell carcinoma of skin, and head and neck cancer may also be increased

EDUCATION, PROPHYLAXIS, AND IMMUNIZATION FOR HIV PATIENTS

EDUCATION AND COUNSELING—patient MUST be told to reveal HIV status to sexual partners (reportable disease). Advise regarding condom use and safer sex practices. Risk reduction strategies should be explored for substance abuse (e.g. avoid sharing needles or other drug paraphernalia), tobacco use, and other social issues. HIV is a chronic disease that can be successfully treated.

PJP PROPHYLAXIS—for patients with CD4 < 200/mm³. Trimethoprim–sulfamethoxazole SS 1 tab PO daily, or trimethoprim–sulfamethoxazole DS 1 tab PO daily, or trimethoprim–sulfamethoxazole DS 1 tab PO three times a week. If allergic, desensitize or use dapsone or inhaled pentamidine

TOXOPLASMOSIS PROPHYLAXIS—for patients with positive Toxoplasma serology and CD4 < 100/mm³. Trimethoprim–sulfamethoxazole DS 1 tab PO daily. If allergic, dapsone plus pyrimethamine plus folinic acid are alternatives

MAC PROPHYLAXIS—for patients with CD4 < 50/mm³. Azithromycin 1200 mg PO once weekly

HISTOPLASMOSIS PROPHYLAXIS—for patients with CD4 < 150/mm³ and living in endemic area. Itraconazole 200 mg PO daily

TB PROPHYLAXIS—for patients with positive TST reaction (induration ≥5 mm) and not treated for TB previously. Isoniazid 5 mg/kg/day PO daily to max 300 mg/day, or 900 mg thrice weekly x 9 months. Rifampin 600 mg PO daily x 4 month restricted to exposures to INH-resistant, RIF-susceptible isolates. Should be followed by a TB specialist

VACCINATIONS

- **GIVE**—Prevnar followed by pneumococcal polysaccharide vaccine at least 8 weeks later. Pneumococcal vaccine should be repeated every 5 years up to three doses. Hepatitis B vaccine (if non-immune), hepatitis A vaccine (if non-immune and especially if homosexual), influenza vaccine annually are all recommended
- **GENERALLY AVOID**—live vaccines (oral polio, varicella, measles-mumps-rubella, or yellow fever immunizations) if CD4 count is <200/mm³

Related Topics
Hepatitis B (p. 145)
Hepatitis C (p. 147)
HIV in Pregnancy (p. 473)
Needle Stick Injury (p. 304)
Tuberculosis (p. 279)
ANTIRETROVIRAL THERAPY FOR HIV PATIENTS

NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)—zidovudine (ZDV, AZT), stavudine (d4T), didanosine (ddI), lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC). Major side effects include hepatic steatosis, lactic acidosis, neuropathy, anemia, pancreatitis, and renal disease.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)—efavirenz (EFV), nevirapine (NVP), etravirine (ETR) and rilpivirine (RPV). Major side effects include rash, Stevens-Johnson syndrome, hepatitis, and CNS complications.

PROTEASE INHIBITORS (PI)—saquinavir (SQV), indinavir (IDV), nelfinavir (NFV), lopinavir–ritonavir (LPV/RTV), fosamprenavir (FPV), atazanavir (ATV), tipranavir (TPV), and darunavir (DRV). Major side effects include hyperglycemia, fat redistribution syndrome, insulin resistance, and GI intolerance.

INTEGRASE INHIBITORS—raltegravir, dolutegravir, elvitegravir.

FUSION INHIBITOR (FI)—enfuvirtide (T-20).

CCR5 ANTAGONIST—maraviroc.

EXAMPLES OF PREFERRED HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) REGIMENS

- NRTI (tenofovir plus emtricitabine) plus NNRTI (efavirenz)
- NRTI (tenofovir plus emtricitabine) plus PI (atazanavir/ritonavir or darunavir/ritonavir)
- NRTI (tenofovir plus emtricitabine) plus integrase inhibitor

THERAPEUTIC DECISIONS IN HIV

GOALS OF HIV THERAPY—durable suppression of HIV viral load to undetectable levels, reduction in HIV related morbidity, improvement in quality of life, prolongation of survival, restoration of immune function, and prevention of HIV transmission.

APPROACH—start treatment in all symptomatic patients and in asymptomatic patients if CD4 < 500/mm³. Treatment should be considered for all patients. Rapidly declining CD4 counts (>100/mm³/year) or baseline viral loads >100,000 copies/mL increase the urgency of treatment. Initiate HIV treatment regardless of CD4 in pregnancy, HIV nephropathy, and in those with HBV when therapy for HBV is indicated. A commitment to lifelong treatment and adherence is essential prior to initiating therapy. HIV therapy is increasingly complex and should only be undertaken by those with expertise in HIV management.

RESPONSE—successful if viral load ↓ by 2 logs after 8 weeks and ↓ to <50 copies/mL after 6 months of therapy. Need to continue therapy or may develop viral load rebound/drug resistance. If failure, consider non-adherence and/or resistance. Resistance testing should be performed, and the regimen should be changed based on resistance profile.

PATHOPHYSIOLOGY—delayed (1 week to several months) inflammatory response as the immune system is restored by antiretrovirals, leading to acute, paradoxical deterioration of pre-existing infections (TB, MAC, PJP, histoplasma, HCV, HBV). Clinical features highly variable. IRIS is a diagnosis of exclusion after considering drug reactions, non-adherence, new onset or progression of opportunistic infection. May occur in up to 25% of patients with opportunistic infections started on HAART (e.g. lymphadenopathy after starting antiretrovirals in patients with disseminated MAC or worsening CXR and fever in patients with TB). In general, treat opportunistic infections for 2 weeks prior to initiating antiretroviral therapy.

TREATMENTS—supportive, continue antiretrovirals, give corticosteroids.

VIRAL HEPATITIS IN HIV CO-INFECTED PATIENTS

HEPATITIS B

- PATHOPHYSIOLOGY—HIV/HBV co-infection rate is up to 20–30% in Asia/sub-Saharan Africa where transmission is mostly vertical or between young children and 5–10% in the USA and Europe where transmission is mostly via IDU and sexual contact. Co-infection is associated with increased risk of progression to end-stage liver disease.
- DIAGNOSIS—for patients with isolated HBCAb, 10–45% have occult HBV infection with detectable levels of HBV DNA.
- PREVENTION—hepatitis B vaccination of family and sexual partners.
- TREATMENT—long-term combination therapy with a nucleoside analogue and nucleotide analogue (e.g. tenofovir plus either emtricitabine or lamivudine) is recommended in co-infected patients. Ultrasound and AFP recommended every 6 months for hepatocellular carcinoma screening.

HEPATITIS C

- PATHOPHYSIOLOGY—HIV/HCV co-infection rate up to 70–95% for patients with IDU and hemo-
Influenza

DIFFERENTIAL DIAGNOSIS

VIRAL—influenza A/B/C, parainfluenza, RSV, metapneumovirus, adenovirus, rhinovirus

BACTERIAL PNEUMONIA—Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus, Moraxella

ATYPICAL—Mycoplasma, Chlamydia, Legionella, TB, community-acquired MRSA

PATHOPHYSIOLOGY

CLASSIFICATION—the three types of influenza are A, B, and C. Influenza A can be classified into various subtypes based on the combination of two surface glycoproteins: neuraminidase (1 of 9 subtypes) and hemagglutinin (1 of 16 subtypes), e.g. H1N1, H1N2, and H3N2. Influenza A subtypes and influenza B can be further classified into various strains that arise due to antigenic drift

HOSTS—influenza B and influenza C viruses mainly affect humans. In contrast, influenza A can infect both humans and animals, including wild birds, poultry, pigs, dogs, and horses. Some influenza A strains are highly pathogenic and can cause severe disease in specific hosts, while others are associated with low pathogenicity. The process whereby at least two different viral strains combine to form a new subtype with a mixture of surface antigens of the original strains is termed antigenic shift and is the source of pandemic influenza virus

ANTIGENIC DRIFT—a gradual change in viral RNA sequence that occurs in both influenza A and B. This process is due to random point mutations in the genes encoding neuraminidase or hemagglutinin, creating strains of virus with new surface glycoproteins. Thus, antibodies against previous strains are ineffective. Can result in seasonal epidemics

ANTIGENIC SHIFT—an abrupt and significant emergence of novel viral strains. Only happens in influenza A. Antigenic shift occurs through mixing of human influenza A and animal (e.g. pig, bird) influenza A virus genes to create a new human influenza A subtype through a process called genetic reassortment (e.g. swine flu, avian flu). Rarely, avian strains of influenza may directly infect humans. Antigenic shift generates new virus and triggers pandemics as the majority of the population has no immunity against this new virus

PANDEMIC (worldwide outbreak)—based on the following criteria: (1) emergence of a new subtype of influenza A virus, (2) this virus is able to infect humans, (3) this virus can spread easily from person to person in a sustained manner

DISTINGUISHING FEATURES BETWEEN INFLUENZA A, B, AND C

| Feature                  | Influenza A | Influenza B | Influenza C |
|--------------------------|-------------|-------------|-------------|
| Hosts                    | Humans, Birds, Mammals | Humans only | Humans, Swine |
| Antigenic shift          | Yes, creating new subtypes | No | No |
| Antigenic drift          | Yes, creating new strains | Yes | Yes |
| Epidemics                | Yes | Yes | No |
| Pandemics                | Yes | No | No |
**CLINICAL FEATURES**

**SYMPTOMS**—acute onset of systemic symptoms, such as fever, headache, myalgia, arthralgia, fatigue, and respiratory symptoms such as cough, dyspnea, and sore throat

**CLINICAL FEATURES (CONT’D)**

**COMPLICATIONS**—respiratory (bacterial pneumonia), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, aseptic meningitis, transverse myelitis, Guillain–Barre syndrome)

**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE INFLUENZA?**

| All age groups | Sens (%) | Spc (%) | LR+ | LR– |
|---------------|----------|---------|-----|-----|
| Fever         | –        | –       | 1.8 | 0.4 |
| Feverishness  | –        | –       | 1.0 | 0.7 |
| Cough         | –        | –       | 1.1 | 0.42|
| Myalgia       | –        | –       | 0.93| 1.2 |
| Malaise       | 73       | 26      | 0.98| 1.1 |
| Headache      | –        | –       | 1.0 | 0.75|
| Sore throat   | –        | –       | 1.0 | 0.96|
| Sneezing      | –        | –       | 1.2 | 0.87|
| Nasal congestion | –     | –       | 1.1 | 0.49|
| Chills        | 83       | 25      | 1.1 | 0.68|
| Vaccine history | –      | –       | 0.63| 1.1 |
| Fever and cough | 64     | 67      | 1.9 | 0.54|
| Fever, cough, and acute onset | 63 | 68 | 2.0 | 0.54|
| Rapid influenza testing | – | – | 4.7 | 0.06|

**Age ≥60**

| Fever         | 34       | 91      | 3.8  | 0.72 |
| Feverishness  | 47       | 78      | 2.1  | 0.68 |
| Cough         | –        | –       | 2.0  | 0.57 |
| Myalgia       | –        | –       | 2.4  | 0.68 |
| Malaise       | 57       | 78      | 2.6  | 0.55 |
| Headache      | –        | –       | 1.9  | 0.70 |
| Sore throat   | –        | –       | 1.4  | 0.77 |
| Sneezing      | 32       | 33      | 0.47 | 2.1 |
| Nasal congestion | 47       | 50      | 0.95 | 1.0 |
| Chills        | 46       | 82      | 2.6  | 0.66 |
| Vaccine history | –      | –       | 0.63 | 1.1 |
| Fever and cough | 30     | 94      | 5.0  | 0.75|
| Fever, cough, and acute onset | 27 | 95 | 5.4 | 0.77|

**APPRAOCH**—“clinical findings identify patients with influenza-like illness but are not particularly useful for confirming or excluding the diagnosis of influenza. Clinicians should use timely epidemiologic data to ascertain if influenza is circulating in their communities, then either treat patients with influenza-like illness empirically or obtain a rapid influenza test to assist with management decisions”

**INVESTIGATIONS**

**BASIC**

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—nasopharyngeal swab for rapid assays (variable sensitivity/specificity), RT-PCR (preferred), or DFA (direct fluorescent antigen detection).

**INVESTIGATIONS (CONT’D)**

- **ANTIGEN DETECTION**
- **MICROBIOLOGY**—nasopharyngeal swab for rapid assays (variable sensitivity/specificity), RT-PCR (preferred), or DFA (direct fluorescent antigen detection). Blood C&S, sputum Gram stain/AFB/C&S, urine C&S
- **IMAGING**—CXR
- **LUMBAR PUNCTURE**—if neurologic symptoms
- **ABG**
MANAGEMENT

PREVENTION IS KEY—annual vaccination for the following individuals: 50 or older, children 6–24 months or taking long-term salicylates, any chronic medical condition, pregnant women, healthcare workers, household contacts of those at risk, and residents of chronic care facilities. In some jurisdictions, universal vaccination for influenza is recommended. Depending on the match between vaccine and circulating virus, the efficacy can range from 70 to 90% for a good match and 0 to 50% for poor matches.

TREATMENT—neuraminidase inhibitors (oseltamivir 75 mg PO BID × 5 days, or zanamivir 10 mg inhaled BID × 5 days) are active against influenza A and B. Antiviral treatment is most effective when started within 48 h of symptom onset. Treatment decreases the duration of symptoms by 1 day, reduces viral shedding, and may reduce complications in those at risk. Inhaled zanamivir is relatively contraindicated in patients with asthma or chronic respiratory conditions. Household contacts of infected individuals should be vaccinated and may be given prophylaxis with oseltamivir.

TREATMENT ISSUES

NEURAMINIDASE INHIBITORS—neuraminidase plays an important role for viral release from the host cell. Oral oseltamivir and inhaled zanamivir are active against both influenza A and B. Antiviral treatment is most effective when started within 48 h of symptom onset. Treatment decreases the duration of symptoms by 1 day, reduces viral shedding, and may reduce complications in those at risk. Inhaled zanamivir is relatively contraindicated in patients with asthma or chronic respiratory conditions. Household contacts of infected individuals should be vaccinated and may be given prophylaxis with oseltamivir.

ADAMANTANES—block replication of influenza A RNA through inhibition of M2 protein ion channels. Amantadine and rimantadine are inactive against influenza B and C and resistance is now widespread in influenza A.

VACCINE PRODUCTION—every February/March, the World Health Organization makes recommendations regarding the three strains (two A and one B) of influenza viruses that are most likely to cause outbreaks in the fall/winter in the upcoming season. Vaccines are then produced based on this decision.

CANDIDIASIS (CONT’D)

75 mg PO daily or zanamivir 10 mg inhaled daily × 10 days. Resistance to oseltamivir is a problem in some strains of influenza A, and amantadine or rimantadine may have a role. Treatment of secondary bacterial pneumonia with antibiotics.

Antiviral Agents

| Antiviral agents | Mechanism | HSV, VZV | CMV | Influenza A | Influenza B |
|------------------|-----------|----------|-----|-------------|-------------|
| Acyclovir        | Nucleoside analogues—activated by viral thymidine kinase, inhibit viral DNA polymerase (vDNAp); also incorporated into viral DNA and act as a chain terminator | ++ |     |             |             |
| 200–800 mg PO BID 5x/day; 5–10 mg/kg IV q8h | | | | | |
| Valacyclovir     | | ++ | | | |
| 500–1000 mg PO daily–TID | | | | | |
| Famciclovir      | | ++ | | | |
| 250–1000 mg PO BID | | | | | |
| Penciclovir      | Applied topically for treatment of oral cold sores | ++ | | | |
### Antiviral Agents (Cont’d)

| Antiviral agents | Mechanism | HSV, VZV | CMV | Influenza A | Influenza B |
|------------------|-----------|----------|-----|-------------|-------------|
| Ganciclovir 5 mg/kg q12h or 1000 mg PO TID (maintenance) | Nucleoside analogue that inhibits viral DNA polymerase | ++ | ++ | | |
| Valganciclovir 900 mg PO daily–BID | | | ++ | +++ | |
| Foscarnet 90 mg/kg IV q12–24 h | Pyrophosphate analogue that inhibits viral DNA polymerase | ++ | +++ | | |
| Cidofovir 5 mg/kg IV q week | Nucleoside analogue that inhibits viral DNA polymerase | ++ | +++ | | |
| Amantadine 100 mg PO BID | Inhibit M2 Protein (ion channel) of influenza A, blocking uncoating of virus genome within newly infected cells | ++ | | | |
| Rimantadine 100 mg PO BID | | | ++ | | |
| Zanamivir 10 mg INH q12–24 h | Neuraminidase Inhibitors. Block release of influenza virus from infected cells | ++ | ++ | | |
| Oseltamivir 75 mg PO daily–BID | | | ++ | ++ | |

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### Fungal Infections

**GENERAL APPROACH**

**CLASSIFICATION**—fungal infections can be classified into three main categories: yeasts, molds (“filamentous fungi”), and dimorphic fungi

- **YEASTS**—grow as single cells (via budding) and include *Candida*, *Malassezia*, *Rodotorula*, *Trichosporon*
- **MOLDS**—these filamentous fungi grow as hyphae (via sexual and asexual reproduction) and include *Aspergillus*, zygomycetes, *Fusarium*, and dematiaceous (pigmented) fungi. Ubiquitous in the environment (e.g. soil, decaying vegetation, water, air). Infection may cause blood vessel invasion, thrombosis, and obstruction. Clinical syndromes include cerebral parenchymal infections, pulmonary parenchymal infections, hepatosplenic abscesses, and otitis externa
GENERAL APPROACH (CONT’D)

- **DIMORPHIC FUNGI**—exist as both molds and yeasts and include *Coccidioides*, *Histoplasma*, *Blastomyces*, and *Cryptococcus*. At low temperatures, found as multicellular molds (which release spores that are inhaled). In warm temperatures (e.g. inside the body), inhaled spores germinate into yeasts, which are contagious to the patient, but no longer contagious (i.e. these patients do not require isolation).

CANDIDIASIS

**PATHOPHYSIOLOGY**—*Candida albicans* ("Germ-tube positive" with pseudohyphae) or non-albicans species ("Germ-tube negative," e.g. *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*), mostly in patients with hematological malignancy, neutropenia, on immunosuppressants, IDU, or those in the intensive care unit with hemodialysis, broad-spectrum antibiotics, surgery, central venous catheters, and parenteral nutrition.

**CLINICAL FEATURES**—localized mucocutaneous infections (thrush and vaginitis), serious focal infections (endophthalmitis, meningitis, osteomyelitis), or disseminated infection (candidemia) with purulent skin lesions, retinal lesions. Candiduria is common in ICU patients, but usually represents colonization unless patient is symptomatic.

**TREATMENTS**

- **OROPHARYNGEAL**— clotrimazole troche 10 mg 5× daily, nystatin suspension (500,000 U) or nystatin pastilles (200,000 U) 4× daily, fluconazole 100 mg PO/IV daily ×1–2 weeks.
- **ESOPHAGITIS**—fluconazole 400 mg loading dose, then 200 mg PO/IV daily ×2–3 weeks.
- **CANDIDURIA**—remove catheter, indications for treatment include kidney transplant recipients, prior to cystoscopy or invasive GU procedure, neonates, severe illness, and possibly neutropenia (controversial). Fluconazole 200 mg PO/IV daily ×2 weeks.
- **ACUTE DISSEMINATED CANDIDEMIA**—remove all intravascular devices. Fluconazole 800 mg IV loading dose, then 400 mg PO/IV daily ×2 weeks (minimum), or one of the echinocandins, including caspofungin 70 mg then 50 mg IV daily, micafungin 100 mg IV daily, or anidulafungin 200 mg loading, then 100 mg IV daily ×2 weeks (minimum) after last positive culture for *C. albicans*. Echinocandin and lipid formulation of amphoterin B are preferred for initial therapy in neutropenic patients. Almost all (>95%) *C. albicans* are sensitive to fluconazole. Some laboratories report *C. albicans* as "C. albicans complex" because of structural resemblance between *albicans* and *dubliniensis*. This is of no clinical significance because *albicans* and *dubliniensis* have the same susceptibility patterns. Susceptibility patterns for other non-albicans infections may significantly differ. Consider echinocandin for non-albicans Candidiasis.

ASPERGILLOSIS

**MICROBIOLOGY**—genus contains >185 species including *A. fumigatus* (80% of clinical infections), *A. flavus*, *A. niger*, and *A. terreus*.

**PATHOPHYSIOLOGY**—mostly in patients with neutropenia, organ or stem cell transplants, advanced AIDS, or on corticosteroids. Invasive aspergillosis has mortality of >50%.

**CLINICAL FEATURES**—spectrum of pulmonary involvement includes colonization, pulmonary aspergilloma ("fungal ball"), allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing aspergillus pneumonia (CNPA), and invasive aspergillosis. Second most common cause of fungal endocarditis (after Candida). Cutaneous involvement may follow trauma or dissemination from respiratory tract.

**DIAGNOSIS**—often difficult and may require biopsy with culture and histology. Check quantitative immunoglobulin, aspergillus IgG and IgE, galactomannan levels (suggestive of invasive aspergillosis). CT chest may show multiple nodular lesions (halo sign = nodule with surrounding hemorrhage, air crescent sign = necrosis and cavitation). Sputum fungal culture and eosinophils, bronchoalveolar lavage, or lung biopsy. The galactomannan assay is relatively specific for invasive aspergillosis, and, in the right clinical context, provides adequate evidence of invasive pulmonary disease. This assay can be done on serum or BAL specimens.

**TREATMENTS**—voriconazole 6 mg/kg q12h ×24 h then 4 mg/kg IV q12h or 200 mg PO BID until resolved. Alternatives include caspofungin 70 mg then 50 mg IV q24h, lipid formulation amphoterin B 3–5 mg/kg IV daily, micafungin 100–150 mg IV daily, posaconazole 200 mg PO QID then 400 mg BID after clinical stabilization. Some species, especially *A. terreus*, are resistant to amphoterin. *Aspergillus* is the only filamentous fungus that can be treated with echinocandins.

CID 2008 46:3
Clin Infect Dis. 2009 49:11
J Clin Microbiol. 2010 48:4
Fungal Infections

**ZYGOMYCETES (MUCORMYCOSIS)**

**MICROBIOLOGY**—large group of filamentous fungi including *Rhizopus*, *Absidia*, *Rhizomucor*, *Mucor*, and *Cunninghamamella*

**PATHOPHYSIOLOGY**—mostly affecting immunocompromised patients and those with diabetes. Prognosis extremely poor

**CLINICAL FEATURES**—CNS, pulmonary, GI, and cutaneous involvement. Infection can cause devastating rhino-orbital-cerebral and pulmonary infections

**TREATMENTS**—antifungal therapy frequently needs to be combined with surgical debridement. Empiric treatment options include lipid formulations of amphotericin B and pozaconazole. Note that susceptibility testing of Zygomycetes is not always reliable, and that caspofungin and “azoles” (apart from pozaconazole) are not generally effective

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**CRYPTOCOCCOSIS**

**MICROBIOLOGY**—formerly believed to be unicellular yeast, although now confirmed to be dimorphic. Unlike other dimorphic fungi (e.g. *Histoplasma*, *Blastomyces*, and *Coccidioides*), *Cryptococcus* is ubiquitous and not geographically isolated. *Cryptococcus neoformans* has two varieties: *C. neoformans var. neoformans* and *var. gattii*

**PATHOPHYSIOLOGY**

- *C. neoformans*—almost invariably in immunocompromised patients including HIV with CD4 < 100/mm³, transplantation, hematologic malignancies, chronic kidney diseases, diabetes mellitus, cirrhosis, or corticosteroid use. This pathogen is inhaled, then disseminates with predilection for CNS with meningitis more common than focal parenchymal infections
- *C. gattii*—seen more commonly in immunocompetent hosts and paradoxically uncommon in immunosuppressed hosts. Symptomatic infection is usually pulmonary ± focal parenchymal brain infection

**CLINICAL FEATURES**—CNS, pulmonary, and cutaneous involvement (but may involve any organ)

**TREATMENTS**—CNS infection (lumbar puncture to lower intracranial pressure, amphotericin B plus flucytosine, followed by fluconazole), pulmonary or cutaneous infection (fluconazole or itraconazole)

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**HISTOPLASMOSIS**

**PATHOPHYSIOLOGY**—*H. capsulatum* endemic along St. Lawrence seaway and in Midwestern states located along the Ohio and Mississippi River valleys. Symptoms typically occur in patients who are immunocompromised or exposed to a large inoculum

**CLINICAL FEATURES**—usually asymptomatic. Pulmonary manifestations may mimic sarcoidosis and include pneumonia (localized or diffuse), granuloma/cavitary lung lesions, and hilar and mediastinal lymphadenopathy. Pericarditis, arthritis, arthralgia and erythema nodosum may also occur without pulmonary symptoms. Disseminated disease may present with hepatosplenomegaly, pancytopenia, oropharyngeal ulcers, skin, and CNS involvement

**DIAGNOSIS**—fungal culture of blood and tissue, urine antigen, *Histoplasma* serology, and histopathology. *Histoplasma* is predominantly an intracellular pathogen; therefore cultures need to be placed in “isolator tube” (containing cell lysis product)

**TREATMENTS**—itraconazole 200 mg PO TID × 3 days, then 200 mg PO daily–BID, lipid formulation of amphotericin B (preferred for ill patients)

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**COCCIDIOIDOMYCOSIS**

**PATHOPHYSIOLOGY**—endemic to lower deserts of southern Arizona, central California, southwestern New Mexico, and west Texas in USA. Also Mexico, Central and South America. Peak incidence from May–July and October–December. Affects mostly patients with immunosuppression

**CLINICAL FEATURES**—an acute pulmonary infection that is often asymptomatic, but can cause a flu-like illness or pneumonia. Pulmonary symptoms include chest pain, cough, fever, and hemoptysis if cavitory lesions. Radiologically, unilateral infiltrate and hilar adenopathy are common. Cutaneous symptoms include erythema nodosum and erythema multiforme. Most common sites of dissemination are skin, bone, and meninges

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**CID 2007 45:7**

**CID 2010 50:3**
**COCIDIOIDOMYCOsis (cont'd)**

**Diagnosis**—fungal culture and serology. Note that *Coccidioides* is a level 3 pathogen. Therefore, cultures should be processed in high-level isolation unit and labeled carefully. There have been numerous reports of iatrogenic infection of laboratory personnel when adequate precautions not taken.

**Treatments**—usually resolves spontaneously if uncomplicated disease. Antifungal therapy may need to be combined with surgery for certain pulmonary infections. *Fluconazole* 400 mg PO daily, *itraconazole* 200 mg PO daily (duration dependent on site of infection and may last months to years). *Coccidioides* meningitis should be treated with amphotericin B.

CID 2005 41:9

**Blastomyces**

**Pathophysiology**—mostly found in northwest Ontario, the Great Lakes, and some Eastern states (e.g. Ohio, Mississippi River valley). Infection occurs by inhalation of aerosolized spores from soil.

**Clinical Features**—asymptomatic infection is common. Pulmonary symptoms of acute or chronic pneumonia (incubation time 45–100 days). Extrapulmonary dissemination to skin, bone/joint, GU tract, usually associated with pulmonary disease.

**Diagnosis**—fungal culture. Presence of “broad-based budding yeast” in clinical specimens strongly suggests *Blastomyces*.

**Treatments**—amphotericin B or lipid formulation for moderate to severe disease or CNS involvement. Itraconazole for mild disease or step-down but has poor blood–brain barrier penetration; alternatives are voriconazole or fluconazole.

CID 2008 46:12

**Indications for Voriconazole**

**Invasive Aspergillosis**—first line treatment for invasive and CNS.

**Invasive Candidiasis**—second or third line treatment for patients who are refractory or intolerant of fluconazole (first line for some).

**Fungemia**—empiric treatment for fungi not yet specified where neither amphotericin B nor fluconazole can be used.

**Febrile Neutropenia**—empiric antifungal treatment for patients with suspected aspergillosis infection.

**Indications for Caspofungin/Micafungin**

**Invasive Aspergillosis**—third line treatment for patients who are refractory or intolerant of voriconazole (first line) or amphotericin B (second line).

**Invasive Candidiasis**—second line treatment for patients who are refractory or intolerant of fluconazole (first line for some).

**Fungemia**—empiric treatment for fungi not yet specified where neither amphotericin B nor fluconazole can be used.

**Febrile Neutropenia**—empiric antifungal treatment.

**Treatment Definitions**

**Refractory**—persistence of positive cultures or lack of clinical response despite ≥5 days of therapy and removal of catheter if applicable.

**Intolerance**—serum creatinine doubling from baseline AND ≥450 μmol/L (≥5.1 mg/dL), tripling of serum creatinine from baseline, creatinine clearance ≤40 mL/min or concomitant administration of nephrotoxins, documented allergy, or intolerable infusion reactions.
## Antifungal Agents

| Mechanism | Candida | Cryptococcus | Aspergillus | Other molds | Dimorphic | Zygomycota | Renal adjustments |
|-----------|---------|--------------|-------------|-------------|-----------|------------|------------------|
| **Azoles** |         |              |             |             |           |            |                  |
| Fluconazole<sup>d</sup> 100–400 mg PO/IV daily | Inhibits CP450 (convert lanosterol to ergosterol on cell membrane) | ++C. alb | +++ | | + | | Yes (dose) |
| Itraconazole<sup>e</sup> 100–200 mg PO daily–BID | | +++ | ++ | ++ | ++ | | No |
| Voriconazole<sup>f</sup> 4 mg/kg IV q12h or 200 mg PO BID | | +++ | +++ | ++Fusa/Scedo | ++ | | No but avoid IV form |
| Posaconazole 200 mg PO QID | | +++ | +++ | +++Fusa | ++ | +++ | No |
| **Amphotericin B<sup>g</sup>** | | | | | | | |
| Amphotericin B 0.3–1 mg/kg IV q24h | Binds to ergosterol on cell wall, causing cell leakage | +++ | +++ | ++ | + | +++ | +++ | Yes (interval) |
| Liposomal AmphoB 3–5 mg/kg IV q24h | | +++ | +++ | ++ | + | +++ | +++ | Yes (interval) |
| AmphoB colloidal dispersion | | +++ | +++ | ++ | + | +++ | +++ | Yes (interval) |
| AmphoB lipid complex 5 mg/kg IV q24h | | +++ | +++ | ++ | + | +++ | +++ | Yes (interval) |
| **Echinocandin**<sup>h</sup> | | | | | | | |
| Caspofungin 70 mg then 50 mg IV q24h | Inhibits synthesis of β-1,3-d-glucan on cell wall | +++ | +++ | +Scedo | +/− | | No |
| Antifungal Agents (Cont’d) |
|---------------------------|
| **Mechanism** | **Candida** | **Cryptococcus** | **Aspergillus** | **Other molds**<sup>a</sup> | **Dimorphic**<sup>b</sup> | **Zygomycota**<sup>c</sup> | **Renal adjustments** |
| Micafungin 150 mg IV q24h | +++ | +++ | No |
| Anidulafungin 200 mg then 100 mg IV q24h | +++ | +++ | No |
| 5-Flucytosine | Inhibits synthesis of DNA (thymidylate synthetase) | +++ | +++ | ++ | Yes (dose) |

<sup>a</sup>other than *Aspergillus, Fusarium, Scedosporium,* and *Pseudallescheria boydii* are all examples of molds

<sup>b</sup>dimorphic fungi include *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Paracoccidioides brasiliensis,* and *Sporothrix schenckii*

<sup>c</sup>zygomycota fungi include *Rhizopus, Mucor,* and *Absidia*

<sup>d</sup>fluconazole is ineffective against some *Candida,* molds, and *Zygomycetes*

<sup>e</sup>itraconazole is ineffective against some *Candida, Scedosporium,* and *Zygomycetes.* It has activity against *Cryptococcus,* but has less CSF penetration than fluconazole

<sup>f</sup>voriconazole is ineffective against some *Candida, Scedosporium,* and *Zygomycetes.* It has activity against *Cryptococcus,* but has less CSF penetration than fluconazole

<sup>g</sup>amphotericin B is ineffective against molds (*Fusarium, Scedosporium, Trichosporum, Aspergillus terreus, C. guilliermondii* and *C. lusitaniae* )

<sup>h</sup>caspofungin is ineffective against *Zygomycetes, Cryptococcus,* and *Fusarium* but probably has activity against other molds
**DEFINITION**—infections acquired in hospital that occur between 48 and 72 h after admission and up to 72 h after discharge (up to 30 days for surgical procedures)

**URINARY TRACT INFECTIONS**—secondary to urinary catheters. Infection rates are 1–5%, up to 100% for long-term catheterization. Complications include cystitis, prostatitis, pyelonephritis, and urosepsis

**VENTILATOR-ASSOCIATED PNEUMONIAS**—secondary to mechanical ventilation (after >48 h, p. 105)

**BACTEREMIA**—secondary to central venous catheters. Infection rates are 3–7%

**SURGICAL SITE INFECTIONS**—secondary to incisions

**PREVENTION STRATEGIES**—hand washing, hand washing, and hand washing! Education, isolation, and surveillance are important. Practice routine/standard/universal precautions with the use of gloves when handling all body fluids except sweat. Always use sterile technique when inserting urinary and central venous catheters. Minimize NG tube insertion and keep patient head of bed 30–45° if intubated

**ISOLATION**

- **AIRBORNE** (negative pressure room with high-efficiency particulate aerator filter, certified N95 respirator for personal protection)—varicella, tuberculosis, measles. Negative pressure room required
- **DROPLET** (mask within 3–6 ft; eye protection)—H. influenzae, N. meningitidis, influenza, RSV, pertussis, parainfluenza, adenovirus, human metapneumovirus and other respiratory viruses
- **CONTACT** (glove, gown, wash hands)—C. difficile, VRE, MRSA, carbapenem-resistant organism (CRO), ESBL

**N. MENINGITIDIS PROPHYLAXIS**

- **CHEMOPROPHYLAXIS**—for exposures in last 7 days with ciprofloxacin 500 mg PO×1 dose or rifampin 600 mg PO BID×2 days can be used to reduce the risk of N. meningitidis in “close contacts.” Vaccines are not recommended for primary prophylaxis post-exposure, but may be useful for epidemic control on a population basis
- **CLOSE CONTACTS**—defined as healthcare workers with direct exposure to respiratory secretions (e.g. mouth-to-mouth resuscitation or intubation), household members, intimate contacts, children in school environments, coworkers in the same office, young adults in dormitories, and recruits in training centers. Not recommended for most medical personnel (i.e. those without direct exposure to patient’s oral secretions) or for casual or indirect contacts (e.g. school or workmates)

**NEEDLE STICK INJURY**

**PREVENTION**—routine/standard/universal precautions (gloves, gowns, masks if risk of exposure of body fluids), never recap needles, education

**PRE-EXPOSURE PROPHYLAXIS**—immunization (hepatitis B vaccine at 0, 1, 6 months)

**RISK OF TRANSMISSION**—depends on the mechanism of exposure, source patient characteristics, pre and post-exposure prophylaxis

- **HBV**—6–30% if source positive. Transmission via urine, feces, and saliva unlikely
- **HCV**—1.8% if source positive. Transmission via urine and feces unlikely
- **HIV**—0.3% if source positive. Transmission via urine, feces, and saliva unlikely

**POST-EXPOSURE PROCEDURE**

- **SOURCE PATIENT TESTING**—HBV, HCV, HIV
- **EXPOSED PERSON BASELINE TESTING**—HBV, HCV, HIV (ELISA, Western), CBCD, lytes, urea, Cr, AST, ALT, ALP, bili
- **HBV PROPHYLAXIS**—HB Ig (only if source patient is HBsAg positive or unknown and the exposed person is unvaccinated) and start vaccination for HBV
- **HIV PROPHYLAXIS**—antiretroviral therapy for 30 days (if source patient HIV positive or source patient unknown and high risk). Therapy may include raltegravir and truvada (tenofovir/emtricitabine). If source patient ARV resistance testing known, post-exposure procedure can be tailored accordingly. Treatment should be started within 4 h
- **COUNSELING**—protective sexual intercourse, hold blood donation and breastfeeding, side effects of prophylactic medication(s), follow-up in 2 weeks

http://www.health.alberta.ca/documents/PEP-Guidelines-2013.pdf

**PROPHYLAXIS FOR OTHER INFECTIOUS AGENTS**—diphtheria (penicillin or erythromycin), pertussis (trimethoprim–sulfa, erythromycin), rabies (rabies immune globulin, vaccine), varicella zoster (varicellazoster immune globulin, vaccine), hepatitis A (immune globulin, vaccine)
# Immunization for Adults

[http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-02-eng.php](http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-02-eng.php)

| Vaccine | Type       | Schedule                  | Indications                                                                 | Contraindications |
|---------|------------|---------------------------|------------------------------------------------------------------------------|-------------------|
| Measles SC | Live       | 0, +1 months (if high risk) | All adults not previously immunized in childhood                             | Preg, immunocomp. |
| Mumps SC  | Live       | 0, +1 months (if high risk) | All adults not previously immunized in childhood                             | Preg, immunocomp. |
| Rubella SC | Live       | 0, +1 months (if high risk) | All adults not previously immunized in childhood                             | Preg, immunocomp. |
| Polio IM/SC | Inactivated | –                         | Not routinely recommended for adults                                          | –                 |
| HBV IM  | Recombinant | 0, +1 months, +6 months   | All adults not previously immunized in childhood, particularly high-risk    | –                 |
| HAV IM  | Inactivated | 0, +6 months              | Travelers (esp. developing world), chronic liver disease (e.g. chronic HCV/ | –                 |
|         |            |                           | HBV), MSM, ?food handlers                                                    |                   |
| Influenza IM | Inactivated | Annually (Oct)            | Adults >50 year, >6 month-50 years with chronic disease, pregnancy,         | Preg, immunocomp. |
|         |            |                           | healthcare workers                                                           |                   |
| Varicella SC | Live       | 0, 1–2 months             | All who have not had chicken pox by adulthood, especially healthcare        | Preg, immunocomp. |
|         |            |                           | workers                                                                      |                   |
| Herpes zoster SC | Live   | 1 dose                    | Adults >60 years. Note this vaccine has higher dose of attenuated virus     | Preg, immunocomp, no history of Varicella |
|         |            |                           | than varicella vaccine                                                       |                   |
| HPV IM  | Recombinant | 0, +1–2 months, +6 months | Females aged 9–26 years (licensed also for males in some countries)       | –                 |
|         |            |                           | Controversial as outcomes data pending                                       |                   |
| Vaccine | Type | Schedule | Indications | Contraindications |
|---------|------|----------|-------------|------------------|
| **Bacterial vaccines** | | | | |
| Pertussis | Cellular | 1 dose | All adults not previously immunized in childhood; single dose of acellular Pertussis vaccine combined with Tetanus/diphtheria (Tdap) recommended for adults aged 19–64 | – |
| Td (tetanus, diphtheria) IM | Toxoid, inactivated | 0, +2 months, +6–12 months, q10 year | All adults not previously immunized in childhood (see Tdap under Pertussis) | – |
| Pneumococcal IM/SC | Polysaccharide | 0, +5 year | Adults >65 years, >6 months–50 years with chronic disease, pregnancy, splenectomy, malignancy, smokers | – |
| Haemophilus type B | Conjugated | 1 dose | Splenectomy | – |
| Meningococcal SC | Polysaccharide | 1 dose | Splenectomy, college dormitory students, lab workers, travelers to endemic areas | – |
PRINCIPLES

RISK FACTORS FOR SPECIFIC ORGANISMS

- **HBV** — household contacts/sexual partners of hepatitis patients, IDU, homosexual, multiple sexual partners, tattoo, piercing, transfusions, healthcare workers (prior to vaccine era), residents/workers of institutions for mentally ill or criminals, birth in endemic country

- **HCV** — sexual partners (controversial), IDU, tattoo, piercing, transfusions, residents/workers of institutions for mentally ill or criminals

CONTRAINDICATIONS

- **ALL VACCINES** — anaphylaxis, severe illness
- **LIVE VACCINES** — pregnancy, immunocompromised (steroids, AIDS but not HIV, malignancies)

SIDE EFFECTS — local erythema, fever

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**PRINCIPLES (CONT’D)**

- **PNEUMOCOCCAL, MENINGOCOCCAL, HAEMOPHILUS INFLUENZAE** — splenectomy