

INFECTIOUS DISEASES

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Fever of Unknown Origin

Infect Dis Clin North Am 2007;21:4

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**

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, Wegener's granulomatosis, 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, gonococcemia, chronic meningococcemia, 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 auto-inflammatory syndrome), **alcoholic hepatitis**, **hematoma**, **factitious fever**

PATHOPHYSIOLOGY

DEFINITIONS

- **FEVER OF UNKNOWN ORIGIN (FUO)**
 - **CLASSIC DEFINITION (1961)**— $\geq 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], duration ≥ 3 weeks, diagnosis uncertain after 7 days of investigation in hospital

PATHOPHYSIOLOGY (CONT'D)

• NEW DEFINITIONS

- **FUO**— $\geq 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], duration ≥ 3 weeks, diagnosis uncertain after 3 days in hospital or three outpatient visits
- **NOSOCOMIAL FUO**—hospitalized patients, $\geq 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], diagnosis uncertain after 3 days and infection not present or incubating on admission
- **IMMUNE-DEFICIENT (NEUTROPENIC) FUO**— $> 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], > 3 days, neutrophil count $\leq 500/\text{mm}^3$. See p. 234 for details
- **HIV-RELATED FUO**—HIV patients, $\geq 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], duration ≥ 3 weeks for outpatients or ≥ 3 days for inpatients
- **FEVER, NYD**—persistent fever that has not yet met the definition for FUO

CLINICAL FEATURES

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

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, CK, serum protein electrophoresis, urinalysis, ESR, CRP, ANA, ENA, RF, C3, C4, ANCA, cryoglobulin

INVESTIGATIONS (CONT'D)

- **MICROBIOLOGY**—blood C&S (including *Mycobacterium*), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, serology (HBV, HCV, HIV, monospot, CMV IgM, endemic fungi)
- **IMAGING**—CXR, echocardiogram (if suspect endocarditis), CT chest/abd/pelvis as guided by symptoms

SPECIAL

- **ECG**
- **TUBERCULIN SKIN TEST**
- **BIOPSY**—affected tissue

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 detail workup; adults who remain undiagnosed have good prognosis

MANAGEMENT

EMPIRIC ANTIBIOTICS—ONLY if suspect infectious etiology and therapy cannot be delayed due to severity of patient's disease (see EMPIRIC ANTIBIOTICS p. 257). In general, therapeutic trials of antimicrobials or steroids are discouraged

TREAT UNDERLYING CAUSE

Fever and Rash**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**—meningococemia (purpura), disseminated gonococcal infection
- **GRAM-NEGATIVE BACILLI**—*Salmonella typhi*, *Pseudomonas* (ecytheme 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
- **VASCULITIS**—Wegener's, polyarteritis nodosa
- **BEHCET'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 states. Ehrlichiosis in midwestern, south-central, and southeastern states. Tularemia in western, southeastern, and south-central states and Canada. Relapsing fever (*Borrelia hermsii*) in mountainous areas of the western USA. 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

CLINICAL FEATURES (CONT'D)

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 marks, 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

SPECIAL

- **LUMBAR PUNCTURE**—if suspect meningococcus
- **SKIN BIOPSY**—dermatology consult
- **INFLAMMATORY WORKUP**—CRP, ANA, ENA, RF

MANAGEMENT

ISOLATION PRECAUTIONS—droplet/airborne plus contact precautions for uncertain diagnosis; for purpura with bacterial sepsis, institute droplet and contact isolation precautions. See p. 269 for more details

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

RICKETTSIAL INFECTIONS (WITHIN NORTH AMERICA)

- **THEMES**—all transmitted by ticks, except Q fever. 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. Rash begins on extremities and moves centrally. 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 one-third. 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

SPECIFIC ENTITIES (CONT'D)

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
 - **STAGE 3 (LATE)**—months to years, mono- or oligoarthritis, acrodermatitis chronica atrophicans (in Europe), progressive encephalitis, dementia. Not amenable to antibiotic therapy
- May develop post-Lyme syndrome with musculoskeletal pain, neurocognitive symptoms, dysesthesias and fatigue

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

SPECIFIC ENTITIES (CONT'D)

- **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 \times 1 dose within 72 h of the tick bite
- **TREATMENTS—stage 1** (*doxycycline* 100 mg PO BID \times 10–21 days, or *cefuroxime* 500 mg PO BID \times 10–21 days). **Lyme carditis** (*ceftriaxone* 2 g IV \times 14–21 days if third degree AV block; otherwise, same as stage I with oral antibiotics). **Neurologic Lyme** (*ceftriaxone* 2 g IV \times 14–21 days). **Lyme arthritis** (*doxycycline* 100 mg BID \times 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

SPECIFIC ENTITIES (CONT'D)

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*) \rightarrow 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, PCR, serology
- **TREATMENTS**—atovaquone plus azithromycin

Related Topic

Exanthematous Lesions (p. 364)

Fever and Joint Pain

See JOINT PAIN AND FEVER (p. 276)

Sepsis

See SEPSIS (p. 97)

Febrile Neutropenia

IDSA Guidelines 2002

DIFFERENTIAL DIAGNOSIS

BACTERIAL

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

VIRAL—HSV, VZV, CMV, EBV, HHV6, enterovirus, RSV

FUNGAL—Candida, Aspergillus, Cryptococcus, Fusarium

REACTIVATION OF LATENT INFECTION—Histoplasma, Coccidioides, Toxoplasma, Tuberculosis

PATHOPHYSIOLOGY

DEFINITION—single temp $>38.3^{\circ}\text{C}$ [101°F] or $>38^{\circ}\text{C}$ [100.4°F] for >1 h, ANC $<0.5 \times 10^9/\text{L}$ or $<1.0 \times 10^9/\text{L}$ + expected nadir $<0.5 \times 10^9/\text{L}$

PATHOPHYSIOLOGY (CONT'D)

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

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**

MANAGEMENT

LOW RISK (ANC $>0.1 \times 10^9/L$, peak temperature $<39^\circ C$ [$102.2^\circ F$], no significant symptoms or signs, no significant comorbidities, nearly normal renal and hepatic function, neutropenia <7 days)—*ciprofloxacin* 500 mg PO BID + *amoxicillin-clavulanate* 500 mg PO q8h. May send home with follow-up

HIGH RISK—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 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 5 days (*fluconazole* 400 mg IV daily, *itraconazole* 200 mg IV daily, *amphotericin B* 0.5–1 mg/kg IV daily over 4 h, *casposfungin* 70 mg on first day followed by 50 mg IV daily)

GCSF SUPPORT—see TREATMENT ISSUES below

MANAGEMENT (CONT'D)

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 $\geq 0.5 \times 10^9/L$ for 2 consecutive days, afebrile for ≥ 48 h, cultures negative, and no obvious signs of infection, or if (2) ANC $< 0.5 \times 10^9/L$ 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
- **IF PERSISTENT FEVER ON DAY 3**
 - **STOP ANTIBIOTICS**—if ANC $\geq 0.5 \times 10^9/L$ for 4–5 consecutive days
 - **CONTINUE ANTIBIOTICS**—if ANC $< 0.5 \times 10^9/L$, 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—*mepredine* 50 mg IV, *acetaminophen* 2 tabs PO, *hydrocortisone* 25 mg IV 30 min before dose, and repeat $\times 1$ 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

TREATMENT ISSUES (CONT'D)

- primary prophylaxis (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 × 10⁹/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

TREATMENT ISSUES (CONT'D)

- 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
- J Clin Oncol 2006 24:19**

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 (including metronidazole for *C. difficile* and amphotericin B/fluconazole for fever >72 h), GCSF. Surgical indications include peritonitis, perforation, persistent GI bleeding, or clinical deterioration

Related Topics

Chemotherapy (p. 226)
 Neutropenia (p. 148)
 Sepsis (p. 97)
 Stem Cell Transplant (p. 180)

Fever with Travel History

NEJM 2002 347:7
<http://www.cdc.gov>

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. pneumoniae*, mycoplasma, Legionella, Q fever, typhoid fever, scrub typhus
- **MYCOBACTERIAL**—tuberculosis
- **VIRAL**—influenza, parainfluenza, metapneumovirus, respiratory syncytial virus, adenovirus, dengue
- **FUNGAL**—histoplasmosis, coccidioidomycosis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **PARASITIC**—malaria, Loeffler's syndrome (migration of larval helminths such as ascaris, strongyloides, and hookworm)

FEVER WITH RASH—see FEVER AND RASH (p. 234)
HEMORRHAGIC FEVER

- **BACTERIAL**—rickettsial, meningococcemia, leptospirosis
- **VIRAL**—dengue, yellow fever, Ebola fever, Lassa fever
- **PARASITIC**—malaria

FEVER WITH SEXUAL OR BLOOD EXPOSURES—syphilis, CMV, EBV, HIV, HBV

- **FEVER WITH EOSINOPHILIA**—parasitic (acute hookworm, ascaris, strongyloides, acute schistosomiasis, visceral larva migrans, lymphatic filariasis, acute trichinosis)

DIFFERENTIAL DIAGNOSIS (CONT'D)

FEVER WITH THROMBOCYTOPENIA—malaria, typhoid fever, dengue shock syndrome, ehrlichiosis, Rocky Mountain spotted fever

ACUTE TRAVELER'S DIARRHEA ± FEVER

- **BACTERIAL**—Enterotoxigenic or enteroaggregative *E. coli*, *Campylobacter jejuni*, *Salmonella*, *Shigella*, *Vibrio*, *Aeromonas*, *Plesiomonas*, *C. difficile*
- **VIRAL**—Caliciviruses (Norwalk, Norwalk-like), rotaviruses, enteroviruses
- **PARASITIC**—*Giardia lamblia*, *Cryptosporidium parvum*, *Entamoeba histolytica*, *Cyclospora cayetanensis*, *Isoospora belli*, *E. polecki*, *Balantidium coli*, *Trichinella spiralis*

CHRONIC TRAVELER'S DIARRHEA ± FEVER

- **BACTERIAL**—Enteroaggregative or enteropathogenic *E. coli*, *C. jejuni*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*, *Aeromonas*, *Plesiomonas*, *C. difficile*, *Tropheryma whipplei*
- **MYCOBACTERIAL**—tuberculosis, *M. avium* complex
- **FUNGAL**—*Paracoccidioides brasiliensis*, *Histoplasma capsulatum*
- **PARASITIC**—*G. lamblia*, *E. histolytica*, *C. 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

www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06vol32/acs-01/index-eng.php

CLINICAL FEATURES

HISTORY—pattern and duration of fever, associated symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache), weight loss, night sweats, travel history (specific itinerary, activities and exposures including food and fresh/saltwater history, incubation period), sexual history, immunization status, antimalarial chemoprophylaxis (medications, degree of adherence), 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 marks, joint examination

INVESTIGATIONS**BASIC**

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, *C. diff* toxin A/B, malaria thick and thin smear (repeat ×1 within 12–24 h if initially negative result), serologies (HIV, dengue, rickettsiae, schistosomiasis, strongyloidiasis, leptospira, HAV, HBV, HCV, Hepatitis E)
- **IMAGING**—CXR, U/S abd guided by symptoms

SPECIAL

- **LUMBAR PUNCTURE**

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

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

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**—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

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—serology, schistosome eggs in feces or urine, biopsy of rectum or bladder
- **TREATMENTS**—praziquantel 20 mg/kg PO q8h \times 2 doses (3 doses for *S. japonicum* and *mekongi*); adjunctive corticosteroids for Katayama fever

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 \rightarrow travel to liver and invade hepatocytes \rightarrow divide and form schizonts which contain merozoites (asymptomatic) \rightarrow rupture after 6–16 days and release merozoites into the bloodstream \rightarrow infect erythrocytes and mature from ring forms to trophozoites to mature schizonts (asexual form) over 48 (*P. vivax*, *P. ovale*, *P. falciparum*) or 72 (*P. malariae*) hours \rightarrow merozoites released from erythrocytes (fever, anemia, lactic acidosis, cytokine release) and infect new red cells \rightarrow 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 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.

SPECIFIC ENTITIES (CONT'D)

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). Atovaquone–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>

- **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

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 \pm 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)—see FEVER AND RASH (p. 234)

LEPTOSPIROSIS

- **PATHOPHYSIOLOGY**—*Leptospira interrogans*, zoonosis more common in tropical areas
- **CLINICAL FEATURES**—history of exposure to freshwater. Fever, headache, myalgia, rash, conjunctival suffusion. May be associated with aseptic meningitis, uveitis, elevated transaminases, jaundice, proteinuria, and microscopic hematuria; fulminant syndrome with jaundice, renal failure, and hemorrhage (Weil's Disease)
- **DIAGNOSIS**—serology; culture of blood, urine, and CSF
- **TREATMENTS**—doxycycline or amoxicillin for mild disease; penicillin/ampicillin or ceftriaxone/cefotaxime IV for severe disease

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

BRUCELLOSIS (undulant fever, Mediterranean fever)

- **PATHOPHYSIOLOGY**—Gram-negative facultative intracellular coccobacilli
- **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

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—blood cultures, serology
- **TREATMENTS**—doxycycline plus streptomycin or rifampin

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/arthralgia. Leukopenia and thrombocytopenia
- **DIAGNOSIS**—serology
- **TREATMENTS**—supportive

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

NEJM 2007 356:8

Pneumonia

See PNEUMONIA (p. 6)

Endocarditis

See ENDOCARDITIS (p. 52)

Meningitis

NEJM 2006 354:1

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*)

DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS (CONT'D)

- **ENCEPHALITIS**—HSV, West Nile, St. Louis, Equine, La Crosse

- **ABSCSS**—bacterial

METABOLIC—thyroid storm

STRUCTURAL

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **CEREBRAL INFARCT**

DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS (CONT'D)

- **TUMOR**
- **PITUITARY APOPLEXY**
- **VASCULAR**—TTP/HUS, lupus, vasculitis, granulomatous angiitis

PATHOPHYSIOLOGY

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*
- **AGE >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*

PATHOPHYSIOLOGY (CONT'D)

- **CSF SHUNT**—*S. aureus*, *S. epidermidis*, aerobic Gram negative bacilli*, diphtheroids
- **BASILAR SKULL FRACTURE**—*S. pneumoniae*, *H. influenzae*, group A Streptococci
*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 herniation, 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	50%	
Nausea and vomiting	30%	
Neck pain	28%	
Physical		
Fever	85%	
Neck stiffness	70%	
Altered mental status	67%	
Focal neurological findings	23%	
Rash	22%	
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%
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%

APPROACH—“absence of all 3 signs of the classic triad of fever, neck stiffness, and altered mental status virtually eliminates a diagnosis of meningitis. Fever is most sensitive of triad, stiff neck and altered mental status second and helpful to exclude meningitis in low risk patients. Kernig and Brudzinski signs appear to have low sensitivity and high specificity. Jolt accentuation of headache may be a useful adjunctive maneuver for patients with fever and headache. In patients at sufficient risk of meningitis, a positive test result may aid in the decision to proceed to lumbar puncture, whereas a negative test result essentially excludes meningitis”

JAMA 1999 282:2

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

INVESTIGATIONS (CONT'D)

- **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, with culture. Suspect viral infection if high lymphocytes, normal glucose, and normal/high protein (NEJM 2006 355:e12)

- **OPENING PRESSURE**—normal is 60–250 mmH₂O. 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 (lymphocytes mainly). Other causes include seizure, intracerebral hemorrhage, tumor, and "traumatic tap" (correct by +1 WBC for every 500–1000 RBCs)
- **XANTHOCHROMIA**—lysed RBC. 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

**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"

LR+

CSF analysis

CSF blood glucose ratio ≤ 0.4	18
CSF glucose > 2.2 mmol/L [> 40 mg/dL]	23
CSF WBC $\geq 500/\mu\text{L}$	15
CSF lactate ≥ 3.5 mmol/L [≥ 32 mg/dL]	21

JAMA 2006 296:16

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

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

NEJM 2001 345:24

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*

NEJM 2004 351:18

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 $\times 4$ 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 **ceftazidime** 2 g IV q8h plus **vancomycin**. If HSV encephalitis, give **acyclovir** 10 mg/kg IV q8h

SPECIFIC ANTIBIOTICS—*S. pneumoniae* (penicillin G or ampicillin if MIC < 0.1 $\mu\text{g/mL}$, ceftriaxone or cefotaxime \pm vancomycin $\times 10$ –14 days if MIC > 1.0 $\mu\text{g/mL}$), *N. meningitidis* (ceftriaxone, penicillin G or ampicillin $\times 7$ days), *L. monocytogenes* (ampicillin or penicillin G, plus gentamicin $\times 14$ –21 days), *H. influenzae* (ampicillin, ceftriaxone, or cefotaxime $\times 7$ days), **Enterobacteriaceae** (ceftriaxone or cefotaxime $\times 7$ days)

SPECIFIC ENTITIES

CHRONIC MENINGITIS (> 4 weeks symptoms and persistent CSF abnormalities)—consider TB, fungal infections, neurosarcoidosis, 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 \rightarrow 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 30 mg/kg/day $\times 14$ days

SPECIFIC ENTITIES (CONT'D)

WEST NILE VIRUS ENCEPHALITIS

- **PATHOPHYSIOLOGY**—flavivirus West Nile virus transmitted by mosquitoes between late spring and early autumn
- **CLINICAL FEATURES**—wide spectrum from asymptomatic to severe neurologic disorder. 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

SPECIFIC ENTITIES (CONT'D)

- serum or cerebrospinal fluid (samples from the acute and convalescent phases, submitted at least two weeks apart)
- **TREATMENTS**—supportive. Prevention is key

Related Topics

- Delirium (p. 380)
- Infection Control (p. 269)

Urinary Tract Infections and Sexually Transmitted Infections

Urol Clin N Am 2008;35:1;
 Can J Infect Dis Med Microbiol 2005;16:6;
www.phac-aspc.gc.ca/std-mts/sti-its/guide-lignesdir-eng.php

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

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 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

CLINICAL FEATURES OF URINARY TRACT INFECTIONS

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS WOMAN HAVE ACUTE UTI?

	LR+	LR-
History		
Dysuria	1.5	0.5
Frequency	1.8	0.6
Hematuria	2.0	0.9
Fever	1.6	0.9
Flank pain	1.1	0.9
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 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

INVESTIGATIONS FOR URINARY TRACT INFECTIONS

BASIC

- **LABS**—CBCD, lytes, Cr/urea
- **MICROBIOLOGY**—urinalysis (nitrite or leukocyte esterase sens 75%, spc 82%), urine C&S (pyuria sens 95%, spc 71%; bacteria sens 40–70%, spc 85–95%). Not necessary if symptomatic uncomplicated UTI)

DIAGNOSTIC ISSUES FOR URINARY TRACT INFECTIONS

NUMBER OF BACTERIA—significant bacteria ($>10^5$ /mL) in clean catch suggests UTI (sens 50%). If using lower threshold to $>10^3$ /mL for women with symptoms, sensitivity increases and specificity only decreases slightly

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

UNCOMPLICATED UTI IN WOMEN—*trimethoprim-sulfamethoxazole* (DS-160/800 mg) 1 tab PO BID \times 3 days, *ciprofloxacin* 250–500 mg PO BID \times 3 days, *levofloxacin* 250–500 mg PO daily \times 3 days, *nitrofurantoin macrocrystals* 50 mg PO QID \times 5–7 days, *nitrofurantoin monohydrate macrocrystals* 100 mg PO BID \times 5–7 days, *amoxicillin-clavulanate* 500 mg PO BID \times 7 days, *fosfomycin trometamol* 3 g PO \times 1 dose

COMPLICATED UTI—treatment duration 7–14 days
RECURRENT UTI (consider below measures if >3 episode of UTI/year)—**daily low-dose prophylaxis** (*trimethoprim-sulfamethoxazole* DS $\frac{1}{2}$ tab PO qhs or 1 tab 3 \times /week \times 6 months, *nitrofurantoin* 50 mg or macrocrystals 100 mg PO qhs \times 6 months), **post-coital prophylaxis** (*trimethoprim-sulfamethoxazole* DS $\frac{1}{2}$ -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 \times 2 days

ACUTE UNCOMPLICATED PYELONEPHRITIS—treat empirically with oral fluoroquinolones \times 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 \times 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 \pm ampicillin, third-generation cephalosporin, or carbapenem)

MANAGEMENT OF URINARY TRACT INFECTIONS (CONT'D)

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 \times 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 \times 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

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 (STIs)

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/gonorrhoea (nucleic acid amplification test, NAAT) or urethral/cervical swab for gonorrhoea culture; offer syphilis and HIV testing
- **TREATMENTS**—anti-gonococcal (*cefixime* 400 mg PO \times 1, *ceftriaxone* 125 mg IM \times 1), anti-chlamydial (*azithromycin* 1 g PO \times 1, or *doxycycline* 100 mg PO BID \times 7 days). If gonorrhoea identified, empirically treat for both gonococcus and chlamydia since dual infection is common. 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

**SEXUALLY TRANSMITTED INFECTIONS (STIs)
(CONT'D)**

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

**SEXUALLY TRANSMITTED INFECTIONS (STIs)
(CONT'D)**

- 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 1° syphilis Sensitive/specific
Molecular testing	PCR	Diagnosis of 1° syphilis. Most sensitive/specific but not readily available
Treponemal serology (presence of Ab against TP)	FTA-ABS TPPA MHA-TP TP-EIA INNO-LIA	Diagnosis of syphilis Sensitive; however, does not differentiate venereal from non-venereal treponematoses
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 pallidum; TPPA, TP particle agglutination assay; VDRL, Venereal Disease Research Laboratory; INNO-LIA, line immunoassay

**SEXUALLY TRANSMITTED INFECTIONS (STIs)
(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

JAMA 2003 290:11

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

**SEXUALLY TRANSMITTED INFECTIONS (STIs)
(CONT'D)**

- 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—outpatients** (*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. **Inpatients** (*doxycycline* 100 mg PO q12h and *cefoxitin* 2 g IV q6h ×14 days, or *clindamycin* 900 mg IV q8h and *gentamicin* 1.5 mg/kg IV q8h ×14 days)

Soft Tissue Infections

NEJM 2004 350:9; NEJM 2007 357:4;
CID 2005 41:10

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 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

INVESTIGATIONS

BASIC

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

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 \times 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 q4–6h \times 7–14 days). For MRSA-associated skin infections, consider *vancomycin* 1–2 g IV q12h, *clindamycin* 600 mg IV TID or 300 mg PO QID, *daptomycin* 4–6 mg/kg IV daily, *tigecycline* 100 mg loading dose, then 50 mg IV q12h, *doxycycline* 100 mg PO BID, *linezolid* 600 mg PO/IV q12h or *quinupristin-dalfopristin* 7.5 mg/kg IV q8–12h. **For mild erysipelas**, consider *penicillin* 500 mg PO QID or *amoxicillin* 500 mg PO TID. **For severe erysipelas** with fevers and **chills**, consider *ceftriaxone* 1 g IV q24h or *cefazolin* 1–2 g IV q8h \times 5–14 days

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)
- **PATHOPHYSIOLOGY (type 1)**—inoculation of ischemic or devitalized tissue \rightarrow host immune system and antibiotics relatively ineffective \rightarrow rapid spreading of infection to surrounding tissue \rightarrow late signs include fever, crepitus, shock \rightarrow complications include compartment syndrome, acute renal failure, sepsis. May be limb or life-threatening. May happen over a few hours
- **ASSOCIATIONS**—host (age $>$ 50, cancer, alcoholism, immunocompromised state, malnutrition, obesity), compromised skin (burns, trauma, postoperative infection), compromised blood vessels (peripheral vascular disease, diabetes)

SPECIFIC ENTITIES (CONT'D)

- **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

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—urgent **surgical debridement** of all necrotic tissue. Consider **IVIG** if significant hypotension in Group A *Streptococcus* necrotizing fasciitis. **Polymicrobial** (cefotaxime 2 g IV q8h plus clindamycin 600–900 mg IV q8h [note: clindamycin inhibits toxic protein production], Piperacillin–tazobactam 4.5 g IV q8h, or ampicillin/penicillin G plus ciprofloxacin plus metronidazole). **Streptococcus** (penicillin G 4 MU IV q4h plus clindamycin 600–900 mg IV q8h)

Osteomyelitis

DIFFERENTIAL DIAGNOSIS

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

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)
- **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 non-invasive testing is unlikely to improve accuracy of diagnosis

CLINICAL FEATURES (CONT'D)

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)

	LR+	LR-
Clinical gestalt		
Clinical judgment	9.2	0.70
Wagner grade >2	5.5	0.54
Physical		
Bone exposure	9.2	0.70
Positive probe to bone finding	6.4	0.39
Ulcer area >2 cm ²	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”

CLINICAL FEATURES (CONT'D)

SYMPTOMS

- **ACUTE OSTEOMYELITIS** (<2 weeks)—typically associated with bone pain, tenderness, warmth, swelling, febrile, and chills. Hip, vertebrae, and pelvis tend to manifest few signs and symptoms
- **SUBACUTE OSTEOMYELITIS** (weeks to few months)—longer duration of above symptoms, but less severe. Over time, draining sinus tracts, deformity, instability, and vascular/neurologic changes may develop
- **CHRONIC OSTEOMYELITIS** (>few months)—similar to subacute osteomyelitis

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), U/S, bone marrow scan, dual tracer scan

SPECIAL

- **ULCER PROBING**
- **BONE BIOPSY**—C&S, AFB, TB culture, fungal culture, histology; generally required for 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, periosteal 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 non-union 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) (sens 72%)

DIAGNOSTIC ISSUES (CONT'D)

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 skin swabs have little correlation with the actual organisms growing inside the bone, except for *S. aureus*

Related Topic

Diabetes Mellitus (p. 337)

MANAGEMENT

HEMATOGENOUS—for vertebral osteomyelitis, need blood and bone cultures, then start empiric antibiotics with *cloxacillin* 2 g IV q4–6h 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 ± *ceftazidime* 2 g IV q8h. 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. Risk factors include extraspinal infection site, urinary tract instrumentation, vascular catheter, hemodialysis, intravenous drug abuse, cancer, and diabetes mellitus

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—severe back pain, limited function, and fever (52%)
- **DIAGNOSIS**—MRI, blood cultures. Bone biopsy generally required for confirmation and microbiological diagnosis to guide therapy
- **TREATMENTS**—*cloxacillin* 2 g IV q4–6h 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

SPECIFIC ENTITIES (CONT'D)

(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. 273)

Tuberculosis: Pulmonary

NEJM 1999 340:5; NEJM 2001 345:3;
NEJM 2004 350:20

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 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. 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

PATHOPHYSIOLOGY (CONT'D)

inhibitors, alcohol abuse, malnutrition, liver or kidney disease, poorly controlled diabetes, smoking, gastrectomy, jejunioileal 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; 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**—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 cavity and less often TST positive

CLINICAL FEATURES (CONT'D)

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

Related Topic

Tuberculosis in Pregnancy (p. 412)

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:

- **≥5 MM**—HIV positive, recent TB contact, CXR signs, prior TB
- **≥10 MM**—other risk factors for infection (endemic, immigrant, aboriginal, homeless, injection drug user, healthcare worker, silicosis, kidney or liver disease, gastrectomy, ileal bypass)
- **≥15 MM**—no risk factors

SPUTUM SMEAR

- **UTILITY**—morning sputum $\times 3$ days (AFB, TB culture), induced sputum if necessary, bronchoscopic lavage if cannot obtain sputum. Three consecutive

DIAGNOSTIC ISSUES (CONT'D)

- 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%)

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

MANAGEMENT

LATENT TB INFECTION—**isoniazid** 300 mg PO daily $\times 6$ –12 months or **rifampin** 600 mg PO daily $\times 4$ months. A "decision to tuberculin test is a decision to treat" with no age cutoff for treatment and regardless of BCG vaccination status. Exclude active TB with sputum culture and CXR before treatment. HIV, immunosuppressed, and newly infected patients should be priority for treatment of latent TB

PRIMARY OR REACTIVATION TB—patients should be isolated in single rooms with negative air pressure. TB therapy should be undertaken in consultation with an expert. Susceptibility testing is necessary to guide treatment. Directly observed treatment (DOT) is the standard of care for all patients. TB therapy consists of an intensive phase of daily therapy followed by a continuation phase of twice- or thrice-weekly therapy. **★RIPE★ Rifampin** 10 mg/kg or 600 mg PO daily, **isoniazid** 5 mg/kg or 300 mg PO daily, **pyrazinamide** 20–25 mg/kg PO daily $\times 8$ weeks. **Ethambutol** 15–20 mg/kg PO daily is added until drug susceptibility results are available. This is followed by isoniazid and rifampin daily, twice weekly, or three times weekly for 16 more weeks. Alternatives include isoniazid, rifampin, pyrazinamide, plus ethambutol or streptomycin 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

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

TREATMENT ISSUES (CONT'D)

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 non-nucleoside reverse transcriptase inhibitors may cause toxic levels of rifampin, which should be replaced by rifabutin)

CANADIAN TUBERCULOSIS STANDARDS—see <http://www.phac-aspc.gc.ca/tbpc-latb/index-eng.php> for more information

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*, viridians group streptococci, enterococcus (Group D strep)
- **β-HEMOLYTIC STREPTOCOCCI**—*S. pyogenes* (Group A strep), *S. agalactiae* (Group B strep), group C, F, G strep
- **OTHERS**—*Abiotrophia*, *Granulicatella* ("nutrient variant Strep"), *Leuconostoc*, *Lactococcus*, *Aerococcus*

ANAEROBIC—*Peptostreptococcus*, *Streptococcus*, *Peptococcus*, *Anaerococcus*

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

GRAM-POSITIVE BACILLI (CONT'D)

SPORE FORMING

- **AEROBIC**—*Bacillus anthrax*, *Bacillus cereus*
- **ANAEROBIC**—*Clostridium perfringens*, *C. difficile*, *C. botulinum*

NON-SPORE FORMING

- **AEROBIC, FACULTATIVE, AEROTOLERANT**—*Corynebacterium/diphtheroids*, *Lactobacillus*, *Listeria*, *Gardnerella*, *Nocardia*
- **ANAEROBIC**—*Actinomyces*, *Propionibacterium*, *Eubacterium*

BRANCHING BACILLI—★**ABCD-LMN**★ *Actinomyces* (acid fast negative), *Bacillus*, *Clostridium*, *Diphtheroids*, *Listeria*, *Lactobacillus*, *Mycobacterium* (Modified and Ziehl–Neelsen acid fast), *Nocardia* (modified acid fast)

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*

GRAM-NEGATIVE BACILLI (CONT'D)

- **GLUCOSE FERMENTING BUT NON-LACTOSE FERMENTING**—*Shigella*, *Salmonella*, *Hafnia*, *Morganella*, *Proteus*, *Yersinia*, *Edwardsiella*, *Vibrio* (oxidase positive), *Aeromonas* (oxidase positive), *Pleisiomonas* (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**, *Pasteurella* (cats), *Capnocytophaga* (dogs), *Kingella**, *Actinobacillus**, *Cardiobacterium**, *Haemophilus** (cocci bacilli, pleomorphic), *Legionella* (BCYE agar), *Campylobacter* (boomerang)

*HACEK organisms in endocarditis

SPECIFIC ORGANISMS

NON-GRAM-STAINABLE—Chlamydia, Mycoplasma, Ureaplasma, Rickettsia, Treponema, Coxiella, Ehrlichia, Mycobacteria

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE

GROUP A STREPTOCOCCAL INFECTIONS—cellulitis, erysipelas, necrotizing fasciitis, pharyngitis, bacteremia, Streptococcal toxic shock syndrome, scarlet fever, acute rheumatic fever (post-streptococcal glomerulonephritis)

STREPTOCOCCUS PNEUMONIAE—may develop resistance to penicillin by altered penicillin-binding protein

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE (CONT'D)

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*†*, *Morganella*†*)

†★**SPICE-M**★ 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

Antibiotics

	Mechanism	Gram positive	Gram negative	Anaerobes	Others	Renal adjustments
Antibiotics						
Penicillins						
Penicillin G 2–4 M units IV q4–6h	Bactericidal, cell wall synthesis inhibition and lysis	++ Strep ++ Strep ++ <i>S. aureus</i>	Meningococcus	++ ++	Syphilis	Yes (dose + interval) Yes (dose + interval) No
Penicillin V 250–500 mg PO TID/QID						
Cloxacillin/nafcillin/oxacillin 1–2 g IV q4–6h						
Amino-Penicillins						
Ampicillin 1–2 g IV q4–6h	Bactericidal, cell wall synthesis inhibition and lysis	+++ Strep/Entero +++ Strep/Entero +++ Strep/Entero	+/-H. flu., +/-E. coli +/-H. flu., +/-E. coli ++H. flu., E. coli	+++ ++	Listeria	Yes (interval) Yes (interval) Yes (interval)
Amoxicillin 250–1000 mg PO BID						
Amox/clavulanate 875/125 mg PO BID						
Anti-pseudomonal Penicillins						
Piperacillin 3–4 g IV q4–6h	Bactericidal, cell wall synthesis inhibition and lysis	++	++Pseudo ++Pseudo/H. flu ++Pseudo ++Pseudo	++ +++ ++ +++		Yes (dose + interval) Yes (dose + interval) Yes (dose + interval) Yes (dose + interval)
Piptrazo 3.375 g q6h–4.5 g IV q8h		++ Staph				
Ticarcillin 3–4 g IV q4–6h		++				
Ticarcillin/clavulanate 3.1 g IV q4–6h						
Monoactam and Carbapenems						
Aztreonam 1–2 g IV q6–8h	Bactericidal, cell wall synthesis inhibition and lysis	+++	+++Pseudo	+++		Yes (dose)
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						
Cefazolin 1–2 g IV q8h	Bactericidal, cell wall synthesis inhibition and lysis	+++	+	+		Yes (interval) Yes (interval)
Cephalexin 250–1000 mg PO QID						
Second-Generation Cephalosporins						
Cefuroxime 750–1500 mg IV q8h	Bactericidal, cell wall synthesis inhibition and lysis	++	++	++		Yes (interval) 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.						
Cefixitin 1–2 g IV q6–8h	Bactericidal, cell wall synthesis inhibition and lysis	+++	+++	++		Yes (interval) Yes (interval)
Cefotaxime 1–2 g IV q6–8h		+++	+++	+++		Yes (interval)
Ceftiozone 1–2 g IV q24h		+++	+++	+++		No
Cefazidime 1 g IV q8–12h		+++	+++Pseudo	+++		Yes (interval)
Cefepime 1–2 g IV q12h		+	+++Pseudo	+++		Yes (interval)
Cefkime 400 mg PO daily		+	+++	+++		Yes (interval)
Ceftibiprole 500 mg IV q8–12h		+++MRSA	+++	+++		Yes (interval)
Aminoglycosides						
Gentamicin 5–7 mg/kg IV q24h	Bactericidal, binds to 30S and 50S ribosomes	Entero (syn) +/-Entero (syn) +/-Entero (syn) Entero (syn)	+Pseudo +++Pseudo +++Pseudo +++Pseudo		AFB, Plague	Yes (dose + interval) Yes (dose + interval) Yes (dose + interval) Yes (dose + interval)
Tobramycin 5–7 mg/kg IV q24h						
Amikacin 7.5 mg/kg q12h						
Streptomycin 15 mg/kg IM or IV q24h						

Antibiotics (cont'd)		Mechanism	Gram positive	Gram negative	Anaerobes	Others	Renal adjustments
Antibiotics							
Fluoroquinolones		Bactericidal; inhibit DNA synthesis through inhibition of DNA gyrase and topoisomerase					
Ciprofloxacin	500 mg PO/400 mg IV BID			+++Pseudo		AFB	Yes (interval)
Norfloxacin	400 mg PO BID			+++			Yes (dose ± interval)
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		Bacteriostatic; binds to 50S ribosomes					
Azithromycin	250 mg PO daily		+	+H. flu/legion +H. flu/legion			No
Clarithromycin	250–500 mg PO BID		+	+Legion		++ <i>Mycoplasma</i> and <i>Chlamydia</i> for all macrolides	Yes (dose)
Tetracyclines		Bacteriostatic; binds to 30S ribosomes					No
Doxycycline	100 mg PO/IV q12h		+	+		+ <i>Chlamydia</i>	No
Minocycline	50–100 mg PO daily–BID		+	+		+ <i>Chlamydia</i>	No
Tetracycline	500 mg PO QID		+++MRSA, VRE	++ <i>Acinetobacter</i>		+ <i>Chlamydia</i>	Avoid
Tigecycline	100 mg IV, then 50 mg q12h					+ <i>Chlamydia</i>	No
Sulfa		Bactericidal; blocks DNA synthesis					
Sulfamethoxazole/Trimethoprim 1–2 SS/DS tab PO BID (also available IV)			+	++ <i>Steno</i> , +PIP			Yes (interval)
Clindamycin		Bacteriostatic; binds to rRNA complex					
Clindamycin	150–450 mg PO QID or 300–600 mg IV q6–12h		++	+++			No
Metronidazole		Bactericidal; DNA breakage					
Metronidazole	500 mg PO/IV q12h		+++		+++C. diff	++protozoa	No
Glycopeptides		Bactericidal; interferes with peptidoglycan and RNA synthesis					
Vancomycin	15 mg/kg IV q12h		+++ <i>S. epidermidis</i> , MRSA, Entero		+++C. diff		Yes (interval)
Oxazolidinones		Bactericidal (Strep) and bacteriostatic (Staph, entero); binds to 50S ribosomes					
Linezolid	600 mg PO/IV q12h		++MRSA, VRE		+	++AFB	No
Streptogramins		Inhibits late + early protein synthesis					
Quinupristin/dalfopristin	7.5 mg/kg IV q8h via central line		++MRSA, VRE (not <i>E. faecalis</i>)		+		No
Lipopeptides		Bactericidal; disrupts cell membrane					
Daptomycin	4–6 mg/kg q24h		++MRSA, VRE		+		Yes (interval)

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 $\mu\text{mol/L}$ [2–4 $\mu\text{g/mL}$] when drug is being given for synergy or uncomplicated infections, 12.6–16.8 $\mu\text{mol/L}$ [6–8 $\mu\text{g/mL}$] for serious Gram-negative infection or sepsis, and 14.7–18.9 $\mu\text{mol/L}$ [7–9 $\mu\text{g/mL}$] for life-threatening infections
- **TROUGH LEVELS**—obtain 0–30 min prior to scheduled dose. Should be <4.2 $\mu\text{mol/L}$ [<2 $\mu\text{g/mL}$] 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

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 q24–48h)

- **START**—monitor serum level 6–14h after first dose. Monitor renal function and ototoxicity q3

ONCE-DAILY GENTAMICIN AND TOBRAMYCIN DOSING (CONT'D)

- **ADJUSTMENTS**—dosing interval (q24–48h) 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 $\mu\text{mol/L}$ [22 $\mu\text{g/mL}$] and trough levels <2.1 $\mu\text{mol/L}$ [<1 $\mu\text{g/mL}$] to prevent toxicity. Peak and trough levels do not need to be monitored)

DOSING 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)= $\text{IBW} + 0.4(\text{BW} - \text{IBW})$

Note: 1 kg=2.2 lbs. See p. 406 for IBW calculation

Related Topic

Drug Eruptions (p. 372)

VANCOMYCIN TOXICITY AND DOSING

TOXICITY—rash, infusion-related red man syndrome, rarely nephrotoxicity (especially combined with aminoglycoside), and ototoxicity. However, serum vancomycin levels do not predict toxicity

LOADING DOSE—15–20 mg/kg (usually 1–1.5 g) IV

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 hour. Monitor only if >14 days in patients with stable renal function and mild/moderate infection, or >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 $\mu\text{mol/L}$ [10–15 $\mu\text{g/mL}$]; adjust to 10.4–13.8 $\mu\text{mol/L}$ [15–20 $\mu\text{g/mL}$] 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/second-generation 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

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT ALLERGIC TO PENICILLIN?

HISTORY—history of penicillin allergy (LR+ 1.9, LR− 0.5)

TYPES OF ALLERGIC REACTIONS

★**ACID**★ Antibody-mediated (IgE), Cytotoxic (antibody-dependent), Immune-complex-mediated, Delayed hypersensitivity reaction

PENICILLIN ALLERGY (CONT'D)

- **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

APPROACH—“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

Approach to Empiric Antibiotics**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 antibiotic treatment except for mild infections. However, the specific organism may not be identified 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

SEPSIS—depending on the suspected source. For pulmonary source, respiratory fluoroquinolone plus ceftriaxone ± vancomycin if community setting, anti-pseudomonal plus ciprofloxacin if hospital setting. For urinary source, ceftriaxone or

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

carbapenem or fluoroquinolone or aminoglycoside. For intra-abdominal source, piperacillin–tazobactam plus aminoglycoside. Duration of treatment is at least 10–14 days with rationalization of antibiotics when susceptibility results available. See p. 97 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. 241 for details

COMMUNITY-ACQUIRED PNEUMONIA (*S. pneumoniae*, *Klebsiella*, *Mycoplasma*)—macrolides ± cefotaxime or respiratory fluoroquinolones. Duration of treatment is usually 7 days. See p. 6 for details

ASPIRATION PNEUMONIA (anaerobes, Staph, GNB)—cefotaxime ± clindamycin or metronidazole. Duration of treatment is usually at least 7 days. See p. 6 for details

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

ICU/VENTILATOR-ASSOCIATED PNEUMONIA (GNB, *Pseudomonas*)—ciprofloxacin plus ceftazidime or piperacillin–tazobactam or carbapenem. Duration of treatment is usually 8 days (p. 94)

ENDOCARDITIS (*S. aureus*, *S. viridans*, *Enterococcus*). Duration of treatment is highly variable. See AHA guidelines and p. 52 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. 122 for details

ANTIBIOTIC-ASSOCIATED DIARRHEA (*C. difficile*)—oral metronidazole. Duration of treatment is 10 days. See p. 123 for details

PERITONITIS/INTRA-ABDOMINAL SEPSIS (coliforms, anaerobes)—piperacillin–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. 148 for further information

URINARY TRACT INFECTION (*E. coli*, *Klebsiella*, *Enterococcus*, *Proteus*, *S. saprophyticus*)—nitrofurantoin, trimethoprim–sulfamethoxazole, ciprofloxacin. Duration of treatment is 3 days if uncomplicated UTI, otherwise 14–21 days. See p. 244 for details

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

CELLULITIS (*Staphylococcus*, *Streptococcus*)—cefazolin, cloxacillin, or cephalixin. Duration of treatment is usually 7–10 days. See p. 247 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. piperacillin–tazobactam; carbapenem). Osteomyelitis likely if ulcer >2 cm² or probe touches bone. See p. 248 for details

NECROTIZING FASCIITIS—surgical treatment is mandatory. For polymicrobial infection, cefotaxime plus clindamycin, piperacillin–tazobactam, or ampicillin/penicillin G plus ciprofloxacin/gentamicin plus metronidazole. For *Streptococcus*, penicillin G plus clindamycin. See p. 247 for details

OSTEOMYELITIS (Gram positive, Gram negative, anaerobes)—for Gram-positive coverage, clindamycin, cefazolin, or vancomycin. For Gram-negative coverage, cefotaxime or ciprofloxacin. For *Pseudomonas*, piperacillin or carbapenem or ceftazidime, plus ciprofloxacin or aminoglycoside. Duration of therapy usually at least 6 weeks. See p. 248 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. 273 for details

Hepatitis B

See HEPATITIS B (p. 130)

Hepatitis C

See HEPATITIS C (p. 131)

Herpes Simplex Virus Infection

See HERPES SIMPLEX VIRUS (p. 366)

Human Immunodeficiency Virus

NEJM 2005 353:16; MMWR 2009 58:RR-4;
www.aidsinfo.nih.gov/Guidelines/

RISK FACTORS FOR HIV

SEXUAL CONTACT—homosexual, heterosexual**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 4–6 weeks, 3 months, and 6 months later. If worrying about window period (2–6 weeks post-exposure), may perform viral load testing

BASIC WORKUP FOR THE NEWLY DIAGNOSED

- **HIV STATUS**—viral load, CD4 count, genotype antiretroviral drug resistance testing
- **BASELINE**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, fasting lipid profile, amylase, lipase, CK, HLA B5701, β hCG, CXR, ECG
- **CO-EXISTING/OPPORTUNISTIC INFECTIONS**—HAV serology, HBV testing (HBsAg, HBsAb, HbcAb. If HBsAg or HbcAb positive, check HBV DNA as well), HCV testing (HCV antibodies, if negative but CD4 <200/mm³ and liver enzymes abnormal, consider HCV RNA testing. If HCV positive, assess genotype \pm liver biopsy), Pap smear, anal screening for HPV in gay men (no consensus yet), *Chlamydia* and gonorrhea screen, RPR (syphilis), TB skin test, toxoplasma serology, CMV serology

NATURAL HISTORY OF HIV

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 q2–8weeks 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

NATURAL HISTORY OF HIV (CONT'D)

- **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%)

CD4 COUNT AND PATHOLOGIES IN HIV PATIENTS

CD4 count (/mm ³)	>500	200–500	100–200	<100
Kaposi sarcoma	+	+	+	+
Bacterial	+	+	+	+
TB	+	+	+	+
HSV	+	+	+	+
Candida		+	+	+
Coccidioides		+	+	+
Histoplasma		+	+	+
PJP			+	+
Cryptococcus				+
Toxoplasma				+
CMV				+
MAC				+
CNS lymphoma				+

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—CBCD, 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. meningitidis*, *S. pneumoniae*, *Listeria*, Gram-negative bacilli
- **VIRAL MENINGITIS** (any CD4)—HSV encephalitis

DIAGNOSIS—CBCD, 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

RESPIRATORY INFECTIONS IN HIV PATIENTS**DIFFERENTIAL DIAGNOSIS**

- **COMMUNITY-ACQUIRED PNEUMONIA** (any CD4)—most common cause is *S. pneumoniae*. Others include *Moraxella*, *H. influenzae*
- **TUBERCULOSIS** (any CD4)—170× increased risk in HIV patients. May be extrapulmonary
- **NON-TB MYCOBACTERIUM**—MAC (CD4 <100/mm³, pulmonary involvement alone is rare, usually disseminated)
- **FUNGAL** (CD4 <500/mm³)—*Histoplasma*, *Coccidioides*, *Cryptococcus*
- **PNEUMOCYSTIS JIROVECI PNEUMONIA** (PJP, CD4 <200/mm³)

DIAGNOSIS—CBCD, lytes, urea, Cr, LDH (↑ in PJP but non-specific), blood C&S and mycobacterial culture, sputum C&S and AFB, ABG, urine C&S, CXR, bronchoscopy (lavage, biopsy)

TREATMENT OF PJP—*trimethoprim-sulfamethoxazole* 15 mg of TMP/kg PO/IV divided q8h daily ×21 days. If severe disease (PaO₂ <70 mmHg), add *prednisone* 40 mg PO BID ×5 days, then 40 mg PO daily ×5 days, then 20 mg PO daily ×11 days. Alternatives to *trimethoprim-sulfamethoxazole* include *dapsone* plus *trimethoprim*, or *clindamycin* plus *primaquine*, *pentamidine* IV. Use *atovaquone* if G6PD deficiency

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-INFECTIOUS**—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—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, lipase, INR, cultures and serologies, U/S 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*

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*
- **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*)

AIDS-ASSOCIATED MALIGNANCIES (CONT'D)

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 and other supportive individuals. Advise regarding condom use and safer sex practices. Risk reduction strategies should be explored for substance abuse (e.g. avoid alcohol use that may cause disinhibition), 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

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 folic 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 tuberculin skin test 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 TIW ×9 months. *Rifampin* 600 mg PO daily ×4 month restricted to exposures to INH-resistant, RIF-susceptible isolates. Should be followed by a TB specialist

VACCINATIONS

- **GIVE**—pneumococcal vaccine every 5 years, hepatitis B vaccine (if non-immune), hepatitis A vaccine (if non-immune and especially if homosexual), influenza vaccine annually
- **GENERALLY AVOID**—live vaccines (oral polio, varicella, measles-mumps-rubella, or yellow fever immunizations)

Related Topics

Hepatitis B (p. 130)

Hepatitis C (p. 131)

HIV in Pregnancy (p. 413)

Needle Stick Injury (p. 269)

Tuberculosis (p. 250)

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). 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

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

CCRS ANTAGONIST—maraviroc

EXAMPLES OF PREFERRED HIGHLY ACTIVE ANTI-RETROVIRAL 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 (raltegravir)

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 <350/mm³. Treatment should be considered for CD4 between 350 and 500/mm³ and is optional for those >500/mm³. 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

THERAPEUTIC DECISIONS IN HIV (CONT'D)

non-adherence and/or resistance. Resistance testing should be performed, and the regimen should be changed based on resistance profile

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) IN HIV PATIENTS

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

VIRAL HEPATITIS IN HIV CO-INFECTED PATIENTS (CONT'D)

- **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

HEPATITIS C

- **PATHOPHYSIOLOGY**—HIV/HCV co-infection rate up to 70–95% for patients with IDU and hemophilia and 1–12% for men who have sex with men. Co-infection results in more aggressive HCV, with more rapid progression to liver failure and hepatocellular carcinoma, particularly if concurrent alcohol use
- **DIAGNOSIS**—rarely may be HCV seronegative requiring PCR testing. Histologic injury as defined by liver biopsy is a much better predictor of clinical outcomes than liver enzymes or HCV viral load and may be useful in selected patients to guide therapy
- **PREVENTION**—risk reduction and safer needle use
- **TREATMENT**—pegylated interferon α plus ribavirin at standard doses. Response rate is about 50% lower than for HCV mono-infection. ddI is contraindicated and AZT use is discouraged in those on ribavirin

NEJM 2007 356:14

Influenza

NEJM 2008 359:24

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

PATHOPHYSIOLOGY (CONT'D)

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.

PATHOPHYSIOLOGY (CONT'D)

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

PATHOPHYSIOLOGY (CONT'D)

influenza may directly infect humans. Antigenic shift generates new virus and triggers pandemics as the majority of the population have 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

	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?

	Sens	Spc	LR+	LR-
All age groups				
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
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

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE INFLUENZA?

	Sens	Sp ^c	LR+	LR-
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

APPROACH—“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”

JAMA 2005 293:8

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). Blood C&S, sputum Gram stain/AFB/C&S, urine C&S
- **IMAGING**—CXR

SPECIAL

- **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 \times 5 days, or *zanamivir* 10 mg inhaled BID \times 5 days) are active against influenza A and B. Antiviral treatment is most effective when started within 48 h of symptom onset. Treatment decreases

MANAGEMENT (CONT'D)

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

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 influenza B

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

Antiviral Agents

Antiviral agents	Mechanism	HSV, VZV	CMV	Influenza A	Influenza B
Acyclovir 200–800 mg PO BID 5x/day; 5–10 mg/kg IV q8h	Nucleoside analogues—activated by viral thymidine kinase, inhibit viral DNA polymerase (vDNAp); also incorporated into viral DNA and act as a chain terminator	++			
Valacyclovir 500–1000 mg PO daily–TID		++			
Famciclovir 250–1000 mg PO BID		++			
Penciclovir 10 mg/g topically q2h x4 days	Applied topically for treatment of oral cold sores	++			
Ganciclovir 5 mg/kg IV 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 q12–24h	Pyrophosphate analogue that inhibits viral DNA polymerase	++	+++		
Cidofovir 5 mg/kg IV qweek	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 q12–24h	Neuraminidase Inhibitors. Block release of influenza virus from infected cells			++	++
Oseltamivir 75 mg PO daily–BID				++	++

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
- **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 infectious 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 pustular skin lesions, retinal lesions. Candiduria is common in ICU patients, but represents colonization only 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* 200 mg PO/IV daily ×2–3 weeks
- **CANDIDURIA**—remove catheter, indications for treatment include kidney transplant recipients,

CANDIDIASIS (CONT'D)

prior to cystoscopy or invasive GU procedure, neotates, severe illness, and possibly neutropenia (controversial). *Fluconazole* 200 mg PO/IV daily $\times 2$ weeks

- **ACUTE DISSEMINATED CANDIDEMIA**—remove all intravascular devices. *Fluconazole* 800 mg then 400 mg PO/IV daily $\times 2$ 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 then 100 mg IV daily $\times 2$ weeks (minimum) after last positive culture for *C. albicans*. Echinocandin and lipid formulation of amphotericin 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 same susceptibility patterns. Susceptibility patterns for other non-*albicans* infections may significantly differ. Consider echinocandin for non-*albicans*

CID 2009 48:5**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

TREATMENTS—*voriconazole* 6 mg/kg q12h $\times 24$ h then 4 mg/kg IV q12h or 200 mg PO BID until resolved. Alternatives include *caspofungin* 70 mg then 50 mg IV

ASPERGILLOSIS (CONT'D)

q24h, lipid-formulation *amphotericin 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 amphotericin. *Aspergillus* is the only filamentous fungus that can be treated with echinocandins

CID 2008 46:3**ZYGOMYCETES (MUCORMYCOSIS)**

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

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 posaconazole. Note that susceptibility testing of Zygomycetes is not always reliable, and that caspofungin and “azoles” (apart from posaconazole) are not generally effective

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 $\times 3$ days, then 200 mg PO daily—BID, lipid formulation of amphotericin B (preferred for ill patients)

CID 2007 45:7

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)

CID 2010 50:3

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 cavitary

COCCIDIOIDOMYCOSIS (CONT'D)

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

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

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

^a other than *Aspergillus*, *Fusarium*, *Scedosporium*, and *Pseudallescheria boydii* are all examples of molds
^b dimorphic fungi include *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, and *Sporothrix schenckii*
^c zygomycota fungi include *Rhizopus*, *Mucor*, and *Absidia*
^d fluconazole is ineffective against some *Candida*, *Molds*, and *Zygomycetes*
^e itraconazole is ineffective against some *Candida*, *Scedosporium*, and *Zygomycetes*. It has activity against *Cryptococcus*, but has less CSF penetration than fluconazole
^f voriconazole is ineffective against some *Candida*, *Scedosporium*, and *Zygomycetes*. It has activity against *Cryptococcus*, but has less CSF penetration than fluconazole
^g amphotericin B is ineffective against molds (*Fusarium*, *Scedosporium*, *Trichosporum*, *Aspergillus terreus*), *C. guilliermondii* and *C. lusitanae*
^h caspofungin is ineffective against *Zygomycetes*, *Cryptococcus*, and *Fusarium* but probably has activity against other molds

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) or amphotericin B (first line for others)

INDICATIONS FOR VORICONAZOLE (CONT'D)

FUNGEMIA—empiric treatment for fungi not yet speciated where neither amphotericin B nor fluconazole can be used

FEBRILE NEUTROPENIA—empiric antifungal treatment for patients intolerant of amphotericin B

INDICATIONS FOR CASPOFUNGIN

INVASIVE ASPERGILLOSIS—third line treatment for patients who are refractory or intolerant of voriconazole (first line) or amphotericin B (second line)

INVASIVE CANDIDIASIS—second or third line treatment for patients who are refractory or intolerant of fluconazole (first line for some) or amphotericin B (first line for others)

FUNGEMIA—empiric treatment for fungi not yet appreciated where neither amphotericin B nor fluconazole can be used

FEBRILE NEUTROPENIA—empiric antifungal treatment for patients intolerant of amphotericin B

TREATMENT DEFINITIONS

REFRACTORY—persistence of positive cultures OR lack of clinical response despite ≥ 5 days of therapy and removal of catheter if applicable

INTOLERANCE—doubling from baseline and serum Cr ≥ 450 $\mu\text{mol/L}$ [≥ 5.1 mg/dL], creatinine clearance ≤ 40 mL/min or concomitant administration of nephrotoxins, tripling of serum creatinine from baseline, documented allergy, or intolerable infusion reactions

Infection Control**NOSOCOMIAL INFECTIONS**

DEFINITION—infections acquired in hospital that occur between 72 h after admission and 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 endotracheal tube insertion (>48 h, p. 94)

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 erect if intubated

ISOLATION

- **AIRBORNE** (negative pressure room with high-efficiency particulate aerator filter, certified N95 respirator for personal protection)—varicella, tuberculosis. Negative pressure room required
- **DROPLET** (mask within 3–6 feet; eye protection)—*H. influenzae*, *N. meningitidis*, influenza, RSV, pertussis
- **CONTACT** (glove, gown, wash hands)—*C. difficile*, VRE, MRSA

N. MENINGITIDIS PROPHYLAXIS

• **CHEMOPROPHYLAXIS**—for exposures in last 7 days with ciprofloxacin 500 mg PO $\times 1$ dose or rifampin 600 mg PO BID $\times 2$ 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

NOSOCOMIAL INFECTIONS (CONT'D)

- **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, influenza)

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 (if source patient HIV positive). Therapy may include zidovudine and lamivudine \pm protease inhibitor such as lopinavir/

NEEDLE STICK INJURY (CONT'D)

ritonavir (if source patient had been treated and drug resistance possible). 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

MMWR 2005 54:RR-9

NEEDLE STICK INJURY (CONT'D)

PROPHYLAXIS FOR OTHER INFECTIOUS AGENTS—diphtheria (penicillin or erythromycin), meningococcal (rifampin, ciprofloxacin, ceftriaxone), pertussis (trimethoprim-sulfa, erythromycin), rabies (rabies immune globulin, vaccine), varicella zoster (varicella-zoster immune globulin, vaccine), hepatitis A (immune globulin, vaccine)

Immunization for Adults

Ann Intern Med 2009 150:1

Vaccine	Type	Schedule	Indications	Contraindications
Viral vaccines				
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 groups for parenteral or sexual exposure, chronic liver disease (e.g. chronic HCV/ HBV), chronic renal disease, healthcare workers, men who have sex with men, household and sexual contacts of those with chronic HBV, those with or evaluated for STDs	–
HAV IM	Inactivated	0, +6 months	Travelers (esp. developing world), chronic liver disease (e.g. chronic HCV/HBV), men who have sex with men, food handlers	–
Influenza IM	Inactivated	Annually (Oct)	Adults >50year, >6 month-50years with chronic disease, pregnancy, healthcare workers	–
Varicella SC	Live	0, 1–2 months	All who have not had chicken pox by adulthood, especially healthcare workers	Preg, immunocomp.
Herpes zoster SC	Live	1 dose	Adults >60years. Note this vaccine has higher dose of attenuated virus than varicella vaccine	Preg, immunocomp, no history of Varicella
HPV IM	Recombinant	0, +1–2 months, +6 months	Females aged 9–26years (licensed also for males in some countries) Controversial as outcomes data pending	–
Bacterial vaccines				
Pertussis	Cellular	1 dose	All adults <i>not</i> 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, q10year	All adults <i>not</i> previously immunized in childhood (see Tdap under Pertussis)	–
Pneumococcal IM/SC	Polysaccharide	0, +5year	Adults >65years, >6 months-50years 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, health-care 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

PRINCIPLES (CONT'D)

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

CONTRAINDICATIONS

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

SIDE EFFECTS—local erythema, fever

Notes