• I have no financial or other fiduciary relationship with any pharmaceutical or medical device manufacturing companies or corporations. I have not received stipends for promotion of any specific drugs or medical devices.

• Thanks to Erich Grant, MMS, PA-C - who graciously allowed me to use his previous lecture as a template for the presentation for this year’s conference.
Objectives

• Describe key aspects of the clinical presentation of blueprint infectious diseases.
• List significant risk factors for each disease.
• State most common and reliable laboratory tests for diagnosing each disease.
• List the TORCH infections that carry significant risk for severe neonatal infection.
• Name the preferred treatments for each disease.
• State prophylactic measures for applicable diseases.
• Describe any significant risks to immunocompromised individuals that these diseases pose.
VIRAL DISEASE
Cytomegalovirus

- Herpes family
- Neonatal infections - TORCH
  - Hepatosplenomegaly, purpura, CNS changes, hearing loss
  - Thought to be #1 cause of congenital neurologic sequelae
- Immunocompetent patients
  - Usually asymptomatic, can have Mono-like illness (most common cause of “heterophile negative” mono)
  - IgM antibody is diagnostic, IgG takes 1-6 weeks.
- Immunocompromised patients
  - AIDS retinitis, pneumonia, meningoencephalitis, chronic diarrhea
    - Leading cause of blindness in AIDS patients
CMV Infections

- **Diagnosis**
  - Gold standard in neonates is viral culture of the urine and saliva obtained within the first two weeks of life. PCR
  - In HIV: real-time PCR, tissue Bx demonstrating viral inclusions + clinical evidence

- **Treatment**
  - Supportive care
    - Prophylactic treatment in HIV patients
  - IV Ganciclovir
    - Used in children and adults with severe disease
  - **Oral valganciclovir**
  - Foscarnet, Cidofovir check for resistance mutations
Epstein Barr Infection

• Member of Herpes family
• Causes infectious mononucleosis
• Transmitted by saliva, incubation period 5-15 days
• Peak age 14-18 years old
• Signs/Symptoms
  – Fever, pharyngitis, malaise, lymphadenopathy (Posterior cervical), rash, splenomegaly
• Consider in strep neg pts sick for > 2 wks
Epstein Barr Infection

• Labs
  – Lymphocytosis with **atypical lymphs**
  – Elevated liver function tests
  – Positive **heterophile antibody**
    • **Monospot**
    • 25% false neg in first week
    • Ok to recheck
  – Positive EBV specific serology, **IgM**
  – If negative, consider HIV, CMV, Hep

• Complications
  – Splenic rupture – **avoid contact sports**
  – Hepatitis, Myocarditis, Thrombocytopenia, Encephalitis

• Treatment
  – Supportive care
  – **Ampicillin may cause a rash**
  – Cochrane review: minimal evidence for benefit of steroids; low quality studies
Herpes Simplex Virus

- Transmission by direct contact with infected secretions
- Recurrent grouped small vesicles on a erythematous base
- Peri-oral (type 1) or peri-genital (type 2)
- Primary Infection
  - Fever, regional lymphadenopathy, aseptic meningitis
  - Recurrences: precipitated by stress, trauma, sun
- Systemic Infection
  - Immunosuppressed patients
  - Proctitis, esophagitis, keratitis
- Neonatal infection: severe sequelae (TORCH)
HSV type 1

- Primary infection (gingivostomatitis) usually in early childhood
- Painful and last 5-10 days
- May become latent in sensory nerve root ganglion – recurrent disease
- Herpetic whitlow - HSV of finger or nail region
HSV type 2

- Genital herpes
- Incubation period 5 days after sexual contact
- Painful, multiple lesions
- May have **systemic symptoms** such as fever and myalgias
- Prodromal paresthesias in recurrent disease may be noted 12-24 hours prior to lesions
Herpes Simplex Virus

• Diagnosis
  – Tzanck smear – old look for multi-nucleated giant cells
  – Direct fluorescent antibody - newer
  – Culture (high false neg)
  – HSV 2 serology

• Treatment
  – Acyclovir
    • IV for encephalitis
  – Famciclovir
  – Valacyclovir
    • Generic now available
Roseola – HSV 6, 7

- 6-24 months
- Incubation 9-10 days
- High fever 3+ days, otherwise well-appearing
- Crisis, Then rash
- +/- URI sx, nodes, fussiness, appetite
- Febrile seizures
Human Papilloma Virus (HPV)

• DNA virus
• Classified by type and risk:
  – 6, 11 = Low risk → dysplasia / respiratory papillomatosis
  – 16, 18 = High risk → cervical / anogenital cancer
  – General rule: types that cause cancer usually don’t cause warts!
    – Vaccination is recommended in boys and girls ages 9-12. Catch up till age 26 for quadrivalent (Gardisil).
• Most infections are transient and resolve on their own, as do cervical abnormalities.
Human Papilloma Virus (HPV)

- Clinical manifestations of genital HPV infection include:
  - Genital warts
  - Cervical cell abnormalities
  - Anogenital cancer
  - Recurrent respiratory papillomatosis – juvenile disease

- Condylomata acuminata
  - Cauliflower-like appearance
  - Skin-colored, pink, or hyperpigmented
  - May be keratotic on skin; generally non-keratinized on mucosal surfaces

- Smooth papules – be aware condylomata lata, molluscum contagiosum

- Flat papules - More commonly found on mucosal surfaces

- Keratotic warts - Thick horny layer that can resemble common warts or seborrheic keratosis
HPV Diagnosis

• Usually made via **visual inspection**
• Cytologic evaluation:
  – Cervical = Pap smear, colposcopy, biopsy
  – Anal = Pap smear, biopsy
  – Respiratory = biopsy
  – Biopsies are recommended with recurrent disease, ulcerating/bleeding lesions, **immunocompromised host**, pigmented lesions
• **Direct testing**
  – Women 21-24 – no HPV co-testing; reflex to HPV if + LSIL, HSIL
  – Women 24-29 – no consensus (ACOG and USPSTF recommend using best clinical judgment; should always reflex if LSIL/HSIL)
  – Women 30-65 – co-testing recommended
Treatments

**Patient-Applied**
- Podofilox 0.5% solution or gel
  - Twice daily for 3 days, then 4 days off
  - May do 4 cycles
- Imiquimod 5% cream (Aldara)
  - One application, 3 times weekly for 16 weeks
  - Wash area 8-10 hours after application

Avoid the above agents (cytotoxic) in pregnancy

**Provider applied**
- Cryotherapy
  - Repeat applications every 1-2 weeks
- Podophyllin resin
  - Apply a small amount to each wart and allow to air dry
  - Treatment may be repeated weekly if needed
- Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%-90%
  - Apply small amount only to warts and allow to dry
  - Treatment may be repeated weekly if needed
- surgery
Influenza

- RNA virus
- **Influenza A** *(subtypes based on hemagglutinin/neuraminidase)* and **B** *(two currently circulating lineages)*
  - Influenzae A highly infectious, institutional settings
  - Influenzae B noted in schools and military
- Spread by respiratory droplets
- Incubation 1-3 days
- Outbreaks every winter
- **Endemic vs epidemic**
Influenza

• Clinical
  – Abrupt onset **fever** (101-106F)
  – Myalgias, headache, nonproductive cough
  – Coryza and sore throat
  – Exam usually normal

• Labs
  – Leukopenia or normal WBC
  – CXR normal
  – **PCR**, direct antigen
Influenza

• Treatment
  – Symptomatic
  – Influenza A > Oseltamivir, Zanamivir
  – Influenza A or B > Oseltamivir, Zanamivir
    • Antivirals reduce duration of symptoms if given within 48 hours
      (<15% of patient present within 48 hours)
  – Antibiotics if secondary bacterial infection
  – Immunization: (everybody!) elderly, respiratory disease, pregnant women, cardiac disease, health care workers, immunosuppressed; avoid FluMist w/ asthma history

• Complications
  – Reye syndrome (Aspirin)
  – Secondary bacterial infections: Pneumonia
Rabies

- Rhabdovirus
- Transmitted by infected saliva
- History of animal bites
  - Bats, bears, skunks, foxes, raccoons
  - Dogs and cats in developing countries
- Bites closest to brain progress most quickly – retrograde axonal transport
- Signs/Symptoms
  - Encephalitic – rage, hyperactivity, hydrophobia, pharyngeal spasms (80%)
  - Paralytic – paresis, sphincter deficit
Distribution of Rabies

400-500 cases per year in NC
## Rabies postexposure prophylaxis

<table>
<thead>
<tr>
<th>Vaccination category</th>
<th>Biologic</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not previously vaccinated</td>
<td>RIG</td>
<td>Total dose is 20 units/kg body weight. As much of the full dose as feasible should be infiltrated around the wound(s) and any remaining given IM.</td>
</tr>
<tr>
<td></td>
<td>Vaccine</td>
<td>Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1 mL, IM (deltoid area), 1 each on days 0, 3, 7 and 14*</td>
</tr>
<tr>
<td>Previously vaccinated</td>
<td>RIG</td>
<td>Not indicated</td>
</tr>
<tr>
<td></td>
<td>Vaccine</td>
<td>HDCV or PCECV 1 mL, IM (deltoid area), 1 each on days 0 and 3</td>
</tr>
</tbody>
</table>

RIG: rabies immune globulin.

* For persons with immunosuppression, rabies postexposure prophylaxis should be administered using all five doses of vaccine on days 0, 3, 7, 14, and 28.

(Post-exposure Prophylaxis)

Did an exposure to rabies potentially occur?
- Did a mammal (animal with fur) bite the patient?
- Did the patient’s open wound, broken skin, or mucous membrane contact saliva or central nervous system tissue from a mammal?
- Did the patient have direct contact with a bat such that a bite or scratch cannot be ruled out?

Yes

High-risk wild animal (Ex. bat, raccoon, skunk, fox, coyote, bobcat, woodchuck)

Available to test?
- Yes
  - Test and start PEP if positive
- No
  - Start PEP promptly

Low-risk wild animal (Ex. squirrel, chipmunk, mouse/rat, rabbit/hare)

No PEP

Healthy and available for quarantine?
- Yes
  - Healthy after 10-day quarantine?
    - Yes
      - No PEP
    - No
      - Symptoms consistent with rabies
        - Start PEP promptly*

- No
  - Start PEP promptly*

Dog, cat, or ferret

Unavailable

Small pocket pet (Ex. guinea pig, rabbit, gerbil, hamster)

Housed exclusively indoors?
- Yes
  - Contact public health authorities
- No
  - No PEP

Livestock or unknown wild animal

*Start PEP promptly means to start without waiting for test results to be conclusive.
Varicella-Zoster Infections

• Acute Varicella (Chicken Pox)
  – Fever, malaise
  – Rash
    • Pruritic, centripetal, papular rash, vesicular and pustular before crusting
    • First lesion is a “drop on rose petal”
    • Lesions in all stages at any given time
  – Incubation period 14-21 days
  – Vaccine – live virus

• Reactivation (Zoster/Shingles)
  – Dermatomal distribution
  – Vesicular rash with preceding pain
Varicella-Zoster
Varicella-Zoster Infections

• Complications
  – Bacterial infection
  – Pneumonia – older patients
  – Encephalitis
  – Post-herpetic neuralgia
  – TORCH ("other")

• Treatment
  – Supportive: lotions, antihistamines
  – Antivirals: Acyclovir (for primary only if >12 yo, chronic skin/lung disease, steroid therapy, ?pregnancy), valacyclovir, famciclovir
  – Immune globulin: pregnancy, immunosuppressed
  – ACIP recommends routine vaccination of all persons aged ≥60 years with 1 dose of zoster vaccine.
    • Persons who report a previous episode of zoster and persons with chronic medical conditions (e.g., chronic renal failure, diabetes mellitus, rheumatoid arthritis, and chronic pulmonary disease) can be vaccinated unless those conditions are contraindications or precautions.
Erythema Infectiosum (Fifth Disease)

- Parvo B-19 - virus
- Vasculitis, slapped cheek appearance, mild or no other Sx
- Lacy rash O/O x 6 mo

- Fairly benign except:
  - Sickle cell anemia – virus can affect RBC production
  - Impaired immune system – anemia
  1. AIDS
  2. Cancer treatments
  3. Anti-rejection drugs used after organ transplants

- Pregnancy-hemolysis in fetus/newborn – TORCH (“other”)
- Myocarditis
Measles (Rubeola)

- Contagious before rash appears
- Contagion by aerosol
- Cough, coryza, conjunctivitis
- Fever, photophobia
- Rash - morbilliform
- Kopliks spots
- Complication: encephalitis, thrombocytopenia, pneumonia, OM

Atypical measles
- Centripetal rash
- Pneumonia
- Abdominal pain, Myalgias
- RISK – incomplete vaccination or killed virus vaccine – waning immunity and exposure to wt
Mumps

- Parotid predilection; usually bilateral
- Respiratory transmission
- Incub: 2-3 wks
- **Orchitis** (tunica albuginea becomes stiff **w/ age**; pressure necrosis)
- **Meningitis**
- Live virus vaccine
Rubella
(German measles)

- Benign illness – immunize because of threat to neonates (Blueberry muffin) - TORCH
- Respiratory transmission
- Incub: 2-3 wks
- Post-auricular nodes
- 3 day rash; arthralgia in females
- Live virus vaccine – do not give if pregnant or immunocompromised
HIV

• Epidemiology
  – Risk factors: sex, injection drug use, transfusions (before screening)
  – CDC rec’s testing age 13-64.

• Etiology
  – Retrovirus
  – Changes viral RNA to viral DNA with aid of reverse transcriptase

• Acute HIV syndrome
  – flu-like illness
HIV Infection Course

Primary infection
Possible acute HIV syndrome
Wide dissemination of virus
Seeding of lymphoid organs

Clinical latency
Opportunistic diseases
 Constitutional symptoms

Death
Plasma Viral Titer
1:512
1:256
1:128
1:64
1:32
1:16
1:8
1:4
1:2
0

Weeks
Years
CD4 T cells/μl
HIV

• Labs
  – Screening **HIV 1,2 Ab and HIV 1 p24 Ag** – early disease
  – If screening + need differentiating Ab test
  – If + on screen and neg on differentiation, proceed w/ NAT
  – Reactive NAT w/ neg or indeterminate Ab differentiation signifies infection w/ HIV 1
  – neg NAT w/ neg or indeterminate Ab differentiation signifies false +
  – Western no longer considered reliable due to frequent misclassification but may still be on test!
  
  – HIV RNA viral load
  – CD4 count
  – ART resistance assay
“AIDS-indicator” diseases

- Candidiasis (esophagus)
- Coccidioides (extrapulmonary)
- Cryptococcus (extrapulmonary)
- Pneumocystis
- CMV (retinitis, colitis, esophagitis, etc.)
- Herpes simplex (chronic/severe)
- Kaposi’s sarcoma; other malignancies
- Cryptosporidium, isospora (chronic)
- Toxoplasma (cerebral)
- Progressive multifocal leukoencephalopathy
- Tuberculosis

- Invasive cervical cancer
- HIV encephalopathy
- Histoplasmosis, disseminated
- Isosporiasis
- Lymphoma
- Lymphoid interstitial pneumonia
- Atypical mycobacterial infection, disseminated
- Recurrent pneumonia
- Salmonella septicemia
- Wasting syndrome
# Prophylaxis Treatment: Opportunistic Infections

**Table 13-10 • Prophylaxis Treatment of Opportunistic Infections in HIV**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Primary Prophylaxis</th>
<th>Alternative Primary</th>
<th>Secondary Prophylaxis</th>
<th>Alternative Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis carinii</em></td>
<td>TMP/SMX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>TMP/SMX</td>
<td></td>
<td>Pyrimethamine plus</td>
<td>Clindamycin plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sulfadiazine plus</td>
<td>pyrimethamine plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>folinic acid</td>
<td>leucovorin</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>INH</td>
<td>Rifabutin plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(INH-sensitive)</td>
<td></td>
<td>pyrazinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Rifampin plus</td>
<td>Rifabutin plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(INH-resistant)</td>
<td>pyrazinamide</td>
<td>pyrazinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium avium complex</em></td>
<td>Azithromycin or</td>
<td>Azithromycin or</td>
<td>Clarithromycin plus</td>
<td>Azithromycin plus</td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
<td>clarithromycin plus</td>
<td>ethambutol</td>
<td>ethambutol</td>
</tr>
<tr>
<td></td>
<td>plus rifabutin</td>
<td>rifabutin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus retinitis</td>
<td></td>
<td>Ganciclovir plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>foscarnet</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td></td>
<td>Fluconazole</td>
<td></td>
<td>Itraconazole</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td></td>
</tr>
</tbody>
</table>
HIV Drugs - ART

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors
- CCR5 antagonists (CCR5s) (also called entry inhibitors)
- Integrase strand transfer inhibitors (INSTIs)
- Choice of regimen is made on individual basis; many are available in combinations
HIV Drugs - ART

• Nucleoside reverse transcriptase inhibitors (NRTIs)
  – Zidovudine (AZT)
  – Lamivudine (3TC)
  – Didanosine (ddI)
  – Stavudine (d4T)
  – Tenofovir (TDF)
  – Abacavir (ABC)
  – Emtricitabine (FTC)

• Side Effects
  – AZT - bone marrow suppression
  – ddI, d4T - peripheral neuropathy, pancreatitis
  – ABC – cardiovascular disease
  – TDF – renal damage
HIV Drugs

• Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  – Nevirapine
  – Delavirdine
  – Efavirenz
  – Etravirine

• Side Effects
  – All can cause a rash
  – Efavirenz causes vivid dreams and is contraindicated in pregnancy
HIV Drugs

- Protease Inhibitors (PIs)
  - Saquinar
  - Ritonavir
  - Indinavir
  - Nelfinavir
  - Darunavir
  - Tipranavir
  - Lopinavir
  - Atazanavir

- Side Effects
  - All can cause nausea, vomiting, and diarrhea
  - Lipodystrophy
  - Indinavir- nephrolithiasis
  - Atazanavir - hyperbilirubinemia
HIV Drugs

- Integrase Inhibitors
  - Raltegravir

- Entry Inhibitors
  - Enfuvirtide
  - Maraviroc
  - Vicriviroc

Newer agents with fewer side effects
BACTERIAL DISEASE
Acute Rheumatic Fever

- Attack against heart valves - most common cause of valve pathology (Molecular mimicry)
- Mitral valve most common valve affected – almost always RF, also aortic, tricuspid
- Group A beta hemolytic streptococci (S. pyogenes) – un/undertreated
**Jones criteria**

**Major Criteria**
- Carditis
- Polyarthritis
- **Sydenham’s chorea**
- Erythema marginatum
- Subcutaneous nodules

**Minor Criteria:**
- Fever
- Arthralgia
- Previous rheumatic fever or rheumatic heart disease
- Acute phase reactants: Leukocytosis, elevated sed rate (ESR) and C-reactive protein (CRP)
- Prolonged P-R interval on electrocardiogram (ECG)

**Need:** two of the major criteria, or one major criterion plus two minor criteria, are present along with **evidence of streptococcal infection** (Anti-Streptolysin-O titer)
Tuberculosis

• Etiology
  – *Mycobacterium tuberculosis*
    • Acid fast bacilli
    – Transmitted by respiratory droplets
    – Most exposed patients do not progress to clinical illness

• Clinical Features
  – Fever, chills, *night sweats*, anorexia, *weight loss*, fatigue, and chronic non-productive cough, *hemoptysis*

• Labs
  – Positive PPD (see next slide)
  – AFB cultures (*Gold standard*) and smears
PPD Interpretation (induration)

- 5mm is positive IF:
  - HIV+
  - On steroid therapy
  - Known close contact with +TB
- >10mm is positive IF:
  - Pt. has DM or renal failure
  - Health care workers
  - IV drug users
  - Prison population
- >15mm is positive IF:
  - No known risks for TB
- Quantiferon gold – highest sens/spec – cannot differentiate latent/active
Tuberculosis

Acid-fast stain showing bacilli

TB lesion
### Dosing regimens for treatment of latent tuberculosis (see text for discussion of clinical approach to selecting a regimen for treatment of latent tuberculosis)

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children &lt;12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Standard regimen: 300 mg PO daily for nine months</td>
<td>Standard regimen: 10 to 15 mg/kg PO daily for nine months; not to exceed 300 mg/day</td>
</tr>
<tr>
<td></td>
<td>Alternate regimen: 300 mg PO daily for six months</td>
<td>Alternate regimen: 20 to 30 mg/kg PO twice weekly for nine months; not to exceed 900 mg/day</td>
</tr>
<tr>
<td></td>
<td>900 mg PO twice weekly for nine months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>900 mg PO twice weekly for six months</td>
<td></td>
</tr>
<tr>
<td><strong>Isoniazid and rifapentine</strong></td>
<td>Isoniazid (orally once weekly for 12 doses, given by direct observation)</td>
<td>(Further study needed)</td>
</tr>
<tr>
<td></td>
<td>15 mg/kg, rounded up to the nearest 50 or 100 mg; 900 mg maximum</td>
<td></td>
</tr>
<tr>
<td>Rifapentine (orally once weekly for three months, given by direct observation)</td>
<td>10 to 14 kg: 300 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.1 to 25 kg: 450 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.1 to 32 kg: 600 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>32.1 to 49.9 kg: 750 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50 kg: 900 mg maximum</td>
<td></td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>600 mg PO daily for four months</td>
<td>10 to 20 mg/kg PO daily for four months; not to exceed 600 mg/day</td>
</tr>
<tr>
<td><strong>Isoniazid and rifapentin</strong></td>
<td>Isoniazid 300 mg PO daily for three months</td>
<td>Isoniazid 10 to 15 mg/kg PO daily for three months; not to exceed 300 mg/day</td>
</tr>
<tr>
<td></td>
<td>Rifampin 600 mg PO daily for three months</td>
<td>Rifampin 10-20 mg/kg PO daily for three months; not to exceed 600 mg/day</td>
</tr>
</tbody>
</table>

* Pyridoxine supplementation (25 to 50 mg PO daily for adults; 1 to 2 mg/kg PO daily for children <12) should be considered for patients on prolonged isoniazid; this is especially important for patients with conditions that can predispose to neuropathy (including diabetes, uremia, alcoholism, malnutrition, and HIV infection), as well as in the setting of pregnancy and seizure disorders. In addition, pyridoxine should be administered to infants of breastfeeding mothers receiving isoniazid. Among children on isoniazid, pyridoxine is warranted for exclusively breastfed infants, children on meat- and milk-deficient diets, children with nutritional deficiencies, and symptomatic HIV-infected children.

* Six-month regimens of isoniazid are not appropriate for children.

Δ Twice-weekly regimens must be administered with directly observed therapy (DOT).

© Patient categories for which this regimen has been studied, and patient categories for which this regimen is NOT appropriate (until further data are available), are discussed in the text. (Refer to UpToDate topic on treatment of latent TB infection in HIV-negative adults, section on isoniazid and rifapentine).

*Adapted from:*

### Drug regimens for active tuberculosis in adults caused by drug-susceptible organisms

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Initial phase</th>
<th>Continuation phase</th>
<th>Range of total doses</th>
<th>Rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drugs</td>
<td>Interval and doses</td>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(minimal duration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Regimen 1</strong></td>
<td>INH RIF PZA EMB</td>
<td>Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)</td>
<td>1a. INH/RIF</td>
<td>Seven days per week for 120 doses (18 wk) or 5 d/wk for 90 doses (18 wk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1b. INH/RIF</td>
<td>Twice weekly for 36 doses (18 wk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1c. INH/RPT</td>
<td>Once weekly for 18 doses (18 wk)</td>
</tr>
<tr>
<td><strong>Regimen 2</strong></td>
<td>INH RIF PZA EMB</td>
<td>Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk), then twice weekly for 12 doses (6 wk)</td>
<td>2a. INH/RIF</td>
<td>Twice weekly for 36 doses (18 wk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2b. INH/RPT</td>
<td>Once weekly for 18 doses (18 wk)</td>
</tr>
<tr>
<td><strong>Regimen 3</strong></td>
<td>INH RIF PZA EMB</td>
<td>Three times weekly for 24 doses (8 wk)</td>
<td>3a. INH/RIF</td>
<td>Three times weekly for 54 doses (18 wk)</td>
</tr>
<tr>
<td><strong>Regimen 4</strong></td>
<td>INH RIF EMB</td>
<td>Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)</td>
<td>4a. INH/RIF</td>
<td>Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4b. INH/RIF</td>
<td>Twice weekly for 62 doses (31 wk)</td>
</tr>
</tbody>
</table>

**Definitions of ratings:**
- A: preferred
- B: acceptable alternative
- C: offer when A and B cannot be given.

*When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.*

*Five-day-a-week administration is always given by DOT.*

*Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the two month specimen, treatment should be extended an extra three months.*

*Data from Am J Respir Crit Care Med 2003; 167:603.*

**EMB:** ethambutol; **INH:** isoniazid; **PZA:** pyrazinamide; **RIF:** rifampin; **RPT:** rifapentine.
TB Drugs: Side Effects

- Isoniazid: hepatitis, *peripheral neuropathy* (Give vitamin B6)
- Rifampin: hepatitis, flu syndrome, *orange body secretions*
- Ethambutol: *optic neuritis* (red-green vision loss)
- Pyrazinamide – *GI/muscle joint pain*
Atypical Mycobacterial Disease

- **Mycobacterium avium** complex
  - Disseminated disease, pulmonary disease, osteo
    - Fever, weight loss, anorexia, diarrhea
  - Seen in HIV / AIDS patients
  - Diagnosis: blood cultures, bone marrow bx
  - Treatment: multiple drugs
    - Rifabutin (Mycobutin), azithromycin, clarithromycin, ethambutol

- **Leprosy**
  - *Mycobacterium leprae*
  - Skin lesions
  - Treatment: months or years (Dapsone, Rifampin, Clofazimine)
Cholera

- Caused by *Vibrio cholerae*, gram (−) comma-shaped rod
- Acute diarrheal illness leading to profound hypovolemia and death
- Epidemics - crowding and famine, Gulf coast
- Acquired from contaminated water and food
- Stool is liquid and gray in color – secretory (rice water stool) – toxin mediated
- Diagnosis
  - Stool culture – gold standard
  - Rapid dipsticks, but poor sens/spec
  - Serology helpful in 1st or 2nd weeks
Cholera

• Treatment
  – Fluids and electrolytes at 50-100mL/kg/hr to start, switch to oral after 4 hours
  – Vaccination if travel to endemic areas (not usually indicated)
  – Antibiotics
    • Single dose doxycycline and many others (macrolides, fluoroquinolones) shorten duration of vibrio excretion
  – 50% of untreated cases are fatal, usually due to dehydration.
Gonococcal Infections

- Venereal disease
  - *Neisseria gonorrhoeae*
- **G (-) diplococci, intracellular**
- Incubation period is 2-8 d
- Purulent profuse *urethral discharge*
- Disseminated disease
  - Fever, skin lesions, tenosynovitis, monoarticular arthritis (knee, ankle, wrist)
- Other sites of infection
  - Conjunctivitis, pharyngitis, proctitis, endocarditis, meningitis
Gonococcal Infections

• Evaluation
  – Gram stain/culture, **NAAT of urine/secretions**
  – HIV, RPR, **Chlamydia**
  – If febrile → joint pains, consider disseminated GC and get blood culture and aspirate painful joint.

• Treatment
  – **Asx**: azithromycin 2 g po
  – **Ceftriaxone 250mg IM x 1**
  – Treat also for Chlamydia, using azithromycin or doxycycline (oral)
  – PID: mild/moderate – ceftriaxone 250, doxy 100 BID x 10 d, +/- metronidazole
  – If disseminated, give ceftriaxone 1g IM or IV until 24-48 hours after clinical improvement
Chlamydia

- **C. trachomatis**: trachoma-worldwide leading cause of blindness; prophylaxis in neonates; reactive arthritis, urethritis, conjunctivitis (Reiter’s syndrome); lymphogranuloma venereum (travel hx, sexual hx)

- **C. Pneumoniae** – atypical pneumonia

- **C. psittaci** – psittacosis pneumonia, inhalation of dried bird “products”
Salmonellosis

- Caused by *Salmonella typhii, typhimurium, enteritidis*
- Transmitted by ingestion of **contaminated foods** (eggs, milk, poultry)
- **Signs/symptoms**
  - Nausea, headache, fever
  - High-volume diarrhea *(pea soup)* but no blood in stool, S. typhii infections usually produce constipation
  - Cramping, abdominal pain 8-48 hours after ingestion
  - Rash: Rose spots (2-3mm papule on trunk)
- **Diagnosis**
  - Normal or low WBC count
  - Stool culture for ID
  - Blood cultures: bacteremia rare
Salmonellosis

• Treatment
  – Fluids and potassium
  – Antibiotics
    • Cipro and ceftriaxone in sickle cell (osteomyelitis) and immunosuppression (AIDS, chemo)
    • Abx not recommended for self-limited non-typhii disease
    • If chronic carrier (stool positive 1 month after resolution of illness) – consult ID
Shigellosis

• Caused by *Shigella sonnei, flexneri*, and *dysenteriae*
• Fecal oral transmission (Day care)
• ~ 3 day incubation period
• Signs/symptoms
  – Fever, malaise, toxic appearing (decrease BP)
  – LLQ cramping abdominal pain with **bloody diarrhea in 50% (dysentery)**
• Labs
  – Positive fecal WBC, **Stool culture**, Blood cultures often positive
• Treatment
  – Supportive care
  – Antibiotics
    • **Based on sensitivity patterns**
      – Ciprofloxacin – first line, ceftriaxone
      – Trimethoprim-sulfamethoxazole; Ampicillin (not amoxicillin)
        » (resistance increasing against both, only use if strain is susceptible)
Botulism

- Gram (+) rod
- *Clostridium botulinum* - neurotoxin
  - A = Western US
  - B = Eastern US
  - E = Alaska
- **Ingestion of home-canned, smoked, or vacuum-packed foods, raw honey**
- **Signs/symptoms**
  - Sudden onset of cranial nerve paralysis, diplopia, dry mouth, dysphagia, dysphonia and progressive muscle weakness
  - **Descending progression, spares sensory nerves**
  - Fixed and dilated pupils in 50%
  - Children: Irritability, weakness, and **hypotonicity**
Botulism

• Diagnosis
  – clinical
  – ID toxin/ culture can take time

• Treatment
  – Removal of toxin from gut via emesis or enema
  – Specific antitoxin (A, B, E most likely)
    • A = Western US
    • B = Eastern US
    • E = Alaska
  – Support (ventilation, nutrition)
  – Penicillin for wounds thought to be source
Tetanus

• Caused by *Clostridium tetani*
  – Found in the soil
  – Incubation 5 days to 15 weeks

• **History of wound** and possible contamination
  – Due to a neurotoxin
  – Blocks inhibitory neurotransmitters

• **Symptoms**
  – Stiffness of neck and other muscles, dysphagia, irritability, hyperreflexia

• **Complications**
  – Airway obstruction
  – Cardiac failure
Tetanus

- Prevention
  - Active immunization (DTaP, Tdap)
  - Passive immunization
    - Tetanus immune globulin

---

**Guide to Tetanus Prophylaxis in Wound Management**

<table>
<thead>
<tr>
<th>History of tetanus immunization</th>
<th>Clean, minor wounds</th>
<th>All other wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertain or &lt; 3 doses of an immunization series**</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>≥ 3 doses received in an immunization series**</td>
<td>No‡</td>
<td>No</td>
</tr>
</tbody>
</table>

Note: Table format changed from previous edition, but recommendations remain unchanged.

* Adult-type tetanus and diphtheria toxoids. If the patient is < 7 years old, a tetanus toxoid-containing vaccine is given as part of the routine childhood immunization.

† Tetanus immune globulin, given at a separate site from Td

** The immunization series for tetanus is described in the text (Schedule and Dosage)

‡ Yes, if > 10 years since last booster.

§ Yes, if > 5 years since last booster. More frequent boosters not required and can be associated with increased adverse events. The bivalent toxoid, Td, is not considered to be significantly more reactogenic than T alone and is recommended for use in this circumstance. The patient should be informed that Td has been given.

¶ Yes, if individuals are known to have a significant humoral immune deficiency state (e.g., HIV, agammaglobulinemia), since immune response to tetanus toxoid may be suboptimal.
Lyme Disease
(Borreliosis)

Most common vector-borne infection in USA
• Vector - Ixodes tick
• Agent: Borrelia burgdorferi
• Spirochete

• Location
  – Massachusetts to Maryland
• Animal Hosts
  – White-footed mouse
  – White tail deer
• Settings
  – Summer months
  – Camping, hunting
Lyme Disease

Erythema migrans

Erythema (chronicum) migrans

Most are not classic target lesions
# Lyme disease Stages

## Stage 1
- flu-like symptoms and skin rash (Erythema migrans)
- (~7% infected persons never develop Sx)

## Stage 2
- About 60% progress to stage II (neuro Sx in 15%):
  - blurred vision, ptosis, fatigue, malaise
  - Arthritis in large joints,
  - muscle pains, stiff neck, loss of muscle function and feeling
  - multiple ECMs

## Stage 2, cont.
- altered consciousness, photophobia, confusion, dyskinesia, Bell's palsy, hallucinations, paresthesia, speech impairment
- Nausea and vomiting

## Stage 3
- 5%
- arthritis
- disease can affect the skin, brain, and nervous system, and muscles, bones, and cartilage.
Lyme Disease

- **Lab**
  - Antibody testing 2 step ELISA followed by western

- **Treatment**
  - Doxycycline
  - Ceftriaxone
  - Penicillin

  **Tick bite:** No treatment

  **Erythema Migrans, Bell’s Palsy:** Doxy 100mg twice daily x 2-3 weeks

  **Other neuro disease:**
  ceftriaxone 2g IV daily or Penicillin G 18-24 million U (both for 2-4 weeks)
Rocky Mountain Spotted Fever

- Due to exposure to tick (*Dermacentor*) bite in endemic area (vector)
- Etiology: *Rickettsia rickettsii*
- Influenza-like prodrome followed by chills, **fever**, severe headache, **myalgias**
- Red, macular rash with onset between 2\textsuperscript{nd} and 6\textsuperscript{th} day of fever
  - Rash on hands- **petechial or purpuric (palms and soles)**
  - Then moves to the center
- Labs
  - Leukocytosis, proteinuria, hematuria, thrombocytopenia
Rocky Mountain spotted fever (RMSF) is caused by Rickettsia rickettsii. Since 2000, the number of reported cases of RMSF has increased during all but a single year. RMSF is reported throughout much of the United States, reflecting the ranges of the primary tick vectors responsible for transmission. Local and regional areas of new or increased reporting and higher incidence are evident in multiple states, including Idaho, Nebraska, North Carolina, and Tennessee.
Rocky Mountain Spotted Fever

• Diagnosis
  – Serologic tests
  – Indirect immunofluorescence assay: *get sample early, then 2-4 weeks later*

• Treatment
  – Don’t delay!
  – *Doxycycline (even in kids!)*
    • Drug of choice
  – Chloramphenicol
Syphilis

• Primary
  – Caused by *Treponema pallidum*
  – History of sexual contact
  – Also a TORCH infection (“other”)
  – Painless ulcer on genitalia, perianal area, rectum, pharynx
    • **Chancre** resolves in 3-6 weeks
  – Enlarged regional lymph nodes
  – Labs: RPR (75-100%), VDRL (75%), FTA-ABS / MHATP (microhemagglutination assay) (90%)
  – Treatment: Benzathine penicillin
    • Doxycycline or tetracycline if PCN allergic
Syphilis

- Secondary (Lues)
  - Generalized maculopapular rash (palms and soles)
  - Condylomata lata
  - Fever, meningitis, hepatitis, arthritis, iritis
  - Labs: VDRL (99%), FTA-ABS (100%)
  - Treatment: same as meds as primary
Syphilis

• Late (Tertiary)
  – Infiltrative tumors (gummae) of skin, bones, liver
  – Aortitis, aneurysms, aortic regurgitation
  – CNS disorders, personality changes
  – Labs: VRDL (75%), FTA-ABS (98%)
  – Treatment: *Penicillin IV x 14 days.*

• Neurosyphilis
  – Can be noted at any time during course of disease
  – Meningitis may present with HA, nausea, vomiting, stiff neck, cranial nerve palsy, hearing loss, Argyll-Robertson pupil, tabes dorsalis
  – Meningovascular meningitis can lead to hemiparesis, hemiplegia, aphasia, and seizures
  – Lab: positive CSF VDRL
  – Treatment: PCN
FUNGAL
Candida albicans

• General
  – Most common opportunistic fungal infection
  – Normal flora in GI and GU tract

• Clinical
  – Oropharyngeal – thrush
  – oral candidiasis in adult, think diabetes, HIV
  – Vulvovaginitis – estrogenized tissue
  – Cutaneous: intertrigo – satellite lesions
Candida albicans

• Diagnosis
  – KOH prep
  – Budding yeast, pseudohyphae
  – Culture

• Treatment
  – Nystatin
  – Fluconazole
  – Miconazole
  – Amphotericin B
    • For disseminated disease
Cryptococcosis

• Most common cause of **fungal meningitis**
  – Organism: *Cryptococcus neoformans*
  – Predisposing factors: **Hodgkin’s, steroid therapy, HIV**

• Symptoms: Headache, mental status changes, meningismus

• Labs:
  – CSF: decrease glucose, increased protein
  – India ink prep
  – Antigen titer

• Also in lungs
  – Broncho-alveolar lavage
  – + culture

• Treatment
  o Oral fluconazole for pulmonary disease
  o Amphotericin B and flucytosine for CNS infection
Histoplasmosis

- *Histoplasma capsulatum* (Dimorphic fungi)
  - Endemic to central and eastern USA, eastern Canada, Mexico and Central America
- Related to bird droppings and bat exposure
  - Inhaled spores
- **Most patients asymptomatic**
  - Mild flu-like to multi-organ disease – mediastinitis, eye, CNS
  - Can resemble TB
- **May disseminate in immunocompromised**
  - Leukemia, steroids, HIV
Histoplasmosis

• Labs
  – RIA/DNA probes
  – Bone marrow positive
  – Increase alk phos, LDH
  – Urine antigen test
  – Skin test
  – CXR: Pneumonia, miliary pattern

• Treatment
  – Itraconazole
  – Amphotericin B
Pneumocystis jiroveci

- In AIDS patients CD4 <200
- Symptoms
  - Fever, dyspnea, nonproductive cough
- CXR
  - Bilateral diffuse interstitial disease without hilar adenopathy
- Exam:
  - Bibasilar crackles or normal
Pneumocystis jiroveci

• Labs
  – Low O$_2$ sats, P$_a$O$_2$
  – Elevated LDH
  – Gallium lung scan: diffuse uptake
  – Lung tissue stains via bronchoscopy
    • (Gold Standard)

• Treatment
  – Bactrim
  – Pentamidine
  – Prednisone if PaO$_2$ <70 mm Hg
Hookworms

- *Necator americanus*
- Moist tropics and **southeastern USA**
- Penetrate skin, migrate in blood to lung, ciliary action brings organism to mouth, swallowed, move to upper bowel, mature and release eggs
- Symptoms
  - Skin penetration: ground itch (tunnels)
  - Lungs: dry cough, blood-tinged sputum
  - GI: anorexia, diarrhea, vague abdominal pain
- Labs
  - Iron deficiency anemia
  - Stool positive for blood
  - O&P
- Treatment
  - Pyrantel
  - Albendazole

Eggs in feces
Ascaris lumbricoides

• Roundworm
  – 2-3 cm long
  – Reside in small intestine

• Oral ingestion
  – Contaminated soil

• Asymptomatic
  – Fever, cough, GI distention

• Labs
  – Eosinophilia
  – O&P

• Treatment
  – Albendazole
Trichuris

- Whipworm
- Southern US
- Poor sanitation; fecal-oral spread thru poor hygiene or unwashed vegetables
- Asymptomatic to diarrhea
- Rectal prolapse with large infestations
- O&P for eggs
Pinworms

- *Enterobius vermicularis*
- Human parasite exclusively
- Anal pruritis
- Usually kids <12 yrs
- **Scotch tape technique** – use **clear** tape
PARASITES
Malaria

• History of travel to endemic area (See next slide)
• Transmitted by Anopheles mosquito
• Episodes of recurring fever, chills and sweating
• Headache, myalgias, splenomegaly, anemia, leukopenia
• Diagnosis: parasites in RBCs on smear (merozoites, schizonts, gametocytes)
  – ‘Thin and thick’ smear is classic
  – New rapid diagnostic test available
Malaria

- Plasmodium
  - Vivax: fever every 48 hours
  - Malariae: every 72 hours
  - Ovale: every 48 hours
  - Falciparum: continuous

- Complications
  - Hemolytic anemia
  - Cerebral malaria
    - P. falciparum
  - Blackwater fever
    - P. falciparum
Malaria

• Treatment
  – Control the vector
  – Medications
    • Atovaquone – for uncomplicated cases
    • artemether-lumefantrine
    • Chloroquine – much resistance
    • Mefloquine
    • Doxycycline - prophylaxis
    • Quinidine gluconate + doxy, tetra, or clindamycin if complicated
Toxoplasmosis

• Caused by *Toxoplasma gondii*
• Cats are the host – *pregnancy concern*
• Infection results from
  – Ingestion of cysts in raw undercooked food
  – Ingestion of contaminated food
  – cat litter
• Signs/Symptoms
  – Asymptomatic
• **TORCH infection**
Toxoplasmosis

• Primary infection - immunosuppression
  – Fever, malaise, headache, lymphadenopathy (cervical), myalgia, arthralgia, stiff neck, sore throat

• Labs
  – Serology
  – CT scan
    • Ring-enhancing lesions

• Treatment
  – Pyrimethamine
    • Plus sulfadiazine
  – Clindamycin as alternative
  – Proper cooking
  – Avoid cat litter