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REFINED CLINICAL REVIEW

FOR THE USMLE STEP 2 & 3

(Third Edition)

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Chapter 1

INFECTIONOUS AND PARASITIC DISEASES

Infectious diseases are among the most common disorders that we encounter in our daily lives. They can affect any organ or system in the body and cause us tremendous losses. Therefore, they deserve adequate attention. While the major pathogens causing particular diseases have not changed much over time, the sensitivity pattern of these microorganisms to antibiotics has changed dramatically in recent years. Culture and sensitivity (C/S) is still the best guide to antibiotic treatment of infectious diseases.

HIGH-YIELD CLINICAL POINTS OF ANTIBIOTICS

1. Antibiotics for Gram$^+$ Cocci

--Staphylococcus (Staph) and Streptococcus (Strep) are the most common organisms.

1. Drugs of choice

(1) Strep-pneumoniae; Strep-hemolytic group A, B, C, G; Strep-viridans: penicillin (PCN)-G, V/K.

(2) Staph, non-penicillinase-producing: PCN; penicillinase-producing Staph: semisynthetic PCN.

(3) Enterococcus faecalis: Ampicillin $\pm$ gentamicin.

(4) Enterococcus faecium: Vancomycin $\pm$ gentamicin.

2. Semisynthetic or penicillinase-resistant penicillins (PRPs):

IV: methicillin, oxacillin, nafcillin; oral (PO): cloxacillin, dicloxacillin, etc. They are highly effective against Staph and Strep, and thus usually used in bacterial skin infections (cellulitis, impetigo), meningitis, endocarditis, osteomyelitis, and septic arthritis. Major adverse effects: anaphylaxis (uncommon).

Methicillin is rarely used clinically due to its renal toxicity. Thus “Methicillin-resistant Staph-aureus” (MRSA) actually refers to “oxacillin- or nafcillin-resistant Staph-aureus.” -- Drug of choice is vancomycin.

3. Replacement for mild penicillin (PCN) allergy:

1$^{\text{st}}$-generation cephalosporins (Ceph): cefazolin, cefadroxil, and cephalaxin. They have good activity against Gram$^+$ bacteria only.

2$^{\text{nd}}$-generation cephalosporins: cefoxitin, cefotetan, cefuroxime, and cefprozil.

Both cephalosporins will cover the same range of organisms as by semisynthetic PCNs.

3$^{\text{rd}}$-generation cephalosporins: ceftazidime, cefotaxime, and ceftriaxone. They are strong against Gram$^-$ bacteria.
4th-generation cephalosporins: cefepime, cefozopran, and cefclidine. They are stronger than the 2nd- and 3rd-generation cephalosporins against most Gram- and some Gram+ bacteria. Cefepime also covers Staph, Strep, and Pseudomonas. PCN-allergy has less than 5% risk of cross-reaction with cephalosporins.

5th-generation cephalosporins: ceftobiprole and ceftaroline. They are the only beta-lactam cephalosporins strongly against MRSA, penicillin-resistant Strep, Pseudomonas, and Enterococci.

Adverse effects of cephalosporins: few, much less hypersensitivity than with PCN; mild GI symptoms; about 10% cross allergy with PCN.

4. Replacement for severe PCN allergy (hypersensitivity):

Macrolides (erythromycin, clarithromycin, azithromycin), fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin), and clindamycin. Macrolides are not choices for serious Staph infections. New quinolones are very effective against both Strep and Staph (but ciprofloxacin does not cover Pneumococcus).

For life-threatening Staph-aureus (MRSA) and Strep-B infection with severe PCN allergy: Strongest antibiotics are vancomycin, synercid, and linezolid.

5. PCN-G, PCN-V/K, ampicillin, and amoxicillin: Effective against Strep (S. pyogenes, S. viridans, and S. pneumonia) and Gram+ bacteria, but not against Staph. Ampicillin and amoxicillin are only effective against Staph when combined with sulbactam or clavulanate; both are effective against Enterococci and Listeria.

II. Antibiotics for Gram- Bacteria

1. Drugs of first choice for Gram- Cocci
   - Moraxella catarrhalis: Cefuroxime
   - Gonococcus: Cefixime, ceftriaxone
   - Meningococcus: PCN, (cefotaxime)

2. Drugs of first choice for Gram- Rods
   - Pseudomonas-A: It’s an opportunistic pathogen that mostly affects immunosuppressed patients.
     **Drugs of choice:** piperacillin-tazobactam or ceftazidime/cefepime, or a carbapenem + gentamicin.
     - Acinetobacter: imipenem, meropenem
     - Bacteroids (GI strains): Metronidazole
     - Campylobacter jejuni: Erythromycin or azithromycin
     - Enterobacter: Ertapenem, imipenem, cefepime
     - E. coli: Uncomplicated—fluoroquinolones, nitrofurantoin; Sepsis—cefotaxime, ceftriaxone
     - Haemophilus: General infection—TMP-SMZ; CNS, serious infection—cefotaxime, ceftriaxone
     - Helicobacter pylori: Amoxicillin + clarithromycin + proton pump inhibitors (PPI)
Klebsiella: A 3rd-generation cephalosporin.

Legionella species (pneumonia): Azithromycin or fluoroquinolones ± rifampin.

Proteus mirabilis: Ampicillin.

3. PCNs (piperacillin, ticarcillin, azlocillin, mezlocillin):

They are strong against the large Enterobacteriaceae group (E. coli, Proteus, Enterobacter, Citrobacter, Morganella, Serratia, and Klebsiella) and Pseudomonas; usually applied for hospital-acquired pneumonia, intra-abdominal infections (cholecystitis, cholangitis, pyelonephritis), bacteremia, neutropenia with fever, etc.

4. Cephalosporins

2nd-generation cephalosporins: Effective against some Enterobacter and Anerobes (cefotetan is the best choice with diabetic ulcerations), but not Pseudomonas.

3rd-generation cephalosporins: Ceftazidime, cefotaxime, and ceftriaxone: Effective against Gram bacilli and the best for PCN-insensitive pneumococcal meningitis or pneumonia.

4th-generation cephalosporins: Only cefepime is effective against Pseudomonas.

5. Quinolones (ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, ofloxacin):

They are active against most of the Enterobacteriaceae; only ciprofloxacin covers Pseudomonas. The new fluoroquinolones (moxifloxacin, levofloxacin, and gatifloxacin) are also strongly effective against Pneumococcus, Mycoplasma, Chlamydia, and Legionella. They are thus the first-line empiric antibiotics for pneumonia.

Adverse effects: bone growth abnormalities in children and pregnant women; cartilage, tendonitis, and Achilles tendon rupture. Gatifloxacin has been associated with (Assoc/w) abnormal glucose metabolism and rarely used now.

6. Aminoglycosides (gentamycin, tobramycin, amikacin) and monobactams (aztreonam):

(1) Effective against the same Gram bacilli as listed above. (2) Synergistic with beta-lactam antibiotics for enterococci and staphylococci. (3) Ineffective against anaerobes. (4) Kidney and ear toxicity.

7. Carbapenems (imipenem, meropenem):

These are strongly active against Enterobacteriaceae and Pseudomonas, plus excellent coverage of Staph and anaerobes. They are effective in polymicrobial infections but are best when used in severe Gram’ infections. Major adverse effects: dose-dependent GI distress.

III. Antibiotics for Anaerobes

1. Metronidazole (Flagyl) is best for abdominal and genital anaerobes.

2. Clindamycin is better for chest anaerobes (Strep).
3. Other choices: Carbapenems, piperacillin + tazobactam, ticarcillin + clavulanate, ampicillin + sulbactam, and amoxicillin + clavulanate are strong medicines for anaerobes. The 2\textsuperscript{nd}-generation cephalosporins (cefoxitin and cefotetan) are also effective.

IV. Antibiotics for Encapsulated Bacteria

These bacteria are more aggressive, including Pneumococcus (Pneumococ), H. Influenza (Hib), Meningococcus (Meningococ), and Klebsiella. Antibiotic choices:

1. New quinolones (Levo-, Moxi-, and Gati-) or the 3\textsuperscript{rd}-generation cephalosporins are the best for Pneumococcus, Meningococcus, and Klebsiella.

2. Ampicillin is the best choice for H. Influenza (and Listeria). Other organisms that ampicillin covers include E coli, Proteus, and Salmonella. Ampicillin is usually a good initial choice for otitis media, preventive use for dental infection or endocarditis, UTI with pregnancy, and limited Lyme disease.

V. Special Antibiotics

(1) Beta-lactam antibiotics --Penicillins, cephalosporins, carbapenems and aztreonam: more effective than most others in the same class.

(2) Vancomycin: Strongly bactericidal against most Gram positives (including Staphylococci, MRSA), anaerobes, diphtheroids, and clostridium species. It’s usually saved for patients allergic to beta-lactam antibiotics, with MRSA or persistent anaerobic infection. Vancomycin should be combined with an aminoglycoside for a complex infection with both Gram\textsuperscript{+} and Gram\textsuperscript{-} bacteria.

(3) Doxycycline: Effective against Chlamydia, limited Lyme disease, Rickettsia, primary and secondary syphilis patients allergic to PCN, Mycoplasma, Borrelia, and Ehrlichia. Adverse effects include tooth discoloration (before age 8), Fanconi syndrome (Type II RTA), photosensitivity, and esophagitis or ulcer.

EYE, EAR, NOSE AND THROAT INFECTIONS

INFECTIONS OF THE EYES

Common eye infections are summarized in Table 1-1.

Table 1-1: Summary of Eye Infections

<table>
<thead>
<tr>
<th>Disease / Clinical features, diagnosis (Dx), and treatment (Tx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious conjunctivitis See Table 1-2.</td>
</tr>
</tbody>
</table>
### Bacterial keratitis

**Features:** Corneal infection caused by foreign body, contact lens and trauma, etc; **hazy cornea** with central ulcers and adjacent stromal abscesses. **Tx:** Refer to an ophthalmologist immediately.

### Fungal keratitis

**Features:** Usually seen in farmers and immunodeficient patient, with vegetable growth on the cornea with multiple stromal abscesses. **Tx:** Refer to an ophthalmologist immediately.

### CMV retinitis

**Features:** #1 common viral infection of the eyes with AIDS or immunodeficiency; **painless retinitis** without conjunctivitis or keratitis. **Funduscopy:** Fluffy/granual retinal lesion with opacity or hemorrhage. Corneal scraping staining (Tzanck test) usually shows multinuclear giant cells. **Tx:** Refer to an ophthalmologist immediately.

### HSV retinitis

**Features:** Painful, with conjunctivitis or keratitis. **Funduscopy:** Retinal pallor, ulcerations or necrosis. Corneal scraping staining usually shows multinuclear giant cells. **Tx:** Refer to an ophthalmologist immediately.

### Orbital cellulitis (Image 18)

**Features:** Peri- or post orbital septum infection; more common in children. Sudden fever, proptosis, painful eyes, decreased eye movement, and red swollen eyelids. **Tx:** Systemic antibiotics.

### Dacryocystitis

**Features:** Infection of the dacryocyst mostly by *Staph-aureus and Strep-B* in > 40 y/o patients; abrupt fever, pain, and redness in the medial canthus, often with purulent discharge and increased WBC. **Tx:** Systemic antibiotics against Staph-aureus and Strep-B.

### Chalazion (Image 19)

**Features:** Also known as meibomian gland lipogranuloma, a granulomatous inflammation of the meibomian gland due to obstruction, changing from painless or painful swelling to a firm nodule on the lid. It often co-exists with rosacea or blepharitis. **Dx** is clinical. **Tx:** 1. Cleaning and compression initially; incision and drainage if necessary. 2. If persistent or recurrent, biopsy is required for suspected squamous cell carcinoma (SCC).

### Hordeolum (Stye, Image 20)

**Features:** Mnemonic: “Horrible Staph”; mostly an abscess caused by *Staph-aureus* infection. Painful, tender swelling localized to the eyelid. Risk factors: smoking and unsanitary behavior. **Dx** is clinical. **Tx:** Warm compression and antibiotics against Staph-A. If ineffective: incision and drainage.

### Infectious Conjunctivitis

It’s an inflammation of the conjunctiva mostly caused by bacteria or viruses. Conjunctivitis can also be caused by chemicals, allergy, fungi, or parasites. Thus the etiologic differentiation is crucial for correct diagnosis (**Dx**) and treatment (**Tx**) to avoid possible loss of vision.

Common infectious conjunctivitis by etiology is summarized in Table 1-2.
Table 1-2: Common Infectious Conjunctivitis

<table>
<thead>
<tr>
<th>Cause / Clinical features, diagnosis, and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral (Image 21)</strong></td>
</tr>
<tr>
<td>Adenovirus is the #1 common virus and occurs in epidemics, with severe ocular irritation, copious watery discharge from the pink/red eye, and pre-auricular lymph node (LN) swelling; highly contagious. Tx: Usually self-limited but contagious. A topical corticosteroid is used if it’s severe.</td>
</tr>
<tr>
<td><strong>Bacterial (Highly contagious)</strong></td>
</tr>
<tr>
<td>Staph, Strep, HIB, Pseudomonas: Foreign body sensation and purulent discharge from the eye. Dx: Gram stain + culture (if severe). Tx: Experienced antibiotic drops and ointment.</td>
</tr>
<tr>
<td><strong>N. gonococcus:</strong> Copious purulent discharge. It may lead to corneal perforation and blindness. Dx: Gram stain shows Gram’ intracellular diplococci. Tx: Emergent IM ceftriaxone; oral ciprofloxacin/ofloxacin. Hospitalization if it’s severe.</td>
</tr>
<tr>
<td><strong>Chlamydial</strong></td>
</tr>
<tr>
<td>C. trachomatis A-C is the #1 cause of chronic conjunctivitis and preventable blindness worldwide. Patient presents with recurrent epithelial keratitis in childhood, with trichiasis, corneal scarring, and entropion. Dx: Giemsa stain and culture for Chlamydia Tx: Azithromycin, tetracycline, or erythromycin for 3-4 weeks.</td>
</tr>
</tbody>
</table>

**Otitis Media**

It’s an infection of the middle ear between the eustachian tube and the tympanic membrane. The most common microorganisms are Pneumococcus, followed by Hib and Moraxella catarrhalis. This organism type is the same as in bronchitis and sinusitis. Viruses cause most other cases of otitis media.

**Essentials of diagnosis**

1. History of ear pain, fever, and decreased hearing.

2. Physical Examination (P/E) reveals a red, bulging tympanic membrane with immobility (No. 1 sign) and loss of the light reflex, with air insufflations. P/E results determine the diagnosis in most cases. Membrane perforation is a rare complication.

**Treatment**

1. Oral amoxicillin is still the best initial therapy.

2. High-dose amoxicillin-clavulanate is used if there has been recent amoxicillin use or resistance. Other alternatives are 2nd or third-generation cephalosporins.

3. Patient with severe penicillin allergies should avoid cephalosporins and take macrolides instead (azithromycin or clarithromycin).

4. If there are multiple recurrences or if there is no response to multiple antibiotics, tympanocentesis should be performed.
Complications and differentiations

1. Membrane perforation or/and hearing loss: It’s the most common complication.
2. Recurrent otitis media: Treatment is antibiotics plus myringotomy and ventilating tubes.
3. Otitis media with effusion: With persistent fluid but few symptoms; usually resolves within 3 months. Treatment is antibiotics along with myringotomy and ventilating tubes.
4. Mastoiditis: Redness and tenderness over the mastoid bone, with an outward and forward displacement of the outer ear. Choose the same antibiotics.
5. Cholesteatoma: A pocket of squamous epithelium in the tympanic membrane. It can spread and destroy other temporal bone structures. Treatment is surgical removal.
7. Labyrinthitis: Vertigo, nystagmus, tinnitus, hearing loss, and vomiting.

Otitis Externa

It’s also known as “Swimmer’s ear”, inflammation of the skin lining the ear canal and surrounding soft tissue. Continuous wetting of the ear canal and local trauma increase the risk. Pseudomonas-A and Staph-aureus are the most common pathogens.

Essentials of diagnosis

1. Ear pruritus and pain exacerbated by moving the ear canal, which is inflamed, swollen, and macerated with purulent discharge.
2. Systemic symptoms may or may not be present.

Treatment

1. Topical antibiotics: Eardrops with polymyxin B, neomycin, and hydrocortisone are very effective. Dicloxacillin is good for acute infection.
2. Patient with diabetes is at increased risk for malignant otitis externa and skull osteomyelitis, requiring IV antibiotics in hospital.
3. Prevention: For frequent swimming activities, use ear spray with dilute alcohol immediately after swimming.

Rhinosinusitis

Rhinitis is a common inflammation of the mucous membrane inside the nose. Non-allergic type can be caused by viruses (Rhinoviruses, Coronaviruses) and bacteria (Pneumococcus, Hib); allergic rhinitis is caused by irritants or allergens. It often coexists with sinusitis, known as rhinosinusitis.

Most patients with rhinitis present with stuffy nose, runny nose, and post-nasal drip. Bacterial rhinitis typically shows mucopurulent nasal discharge. Allergic rhinitis is the most common type, typically showing sneezing, nasal itching and watery discharge, and red itchy eyes (See Chapter 3 for details).
**Sinusitis** is the inflammation of the paranasal sinuses usually due to infection, which is mostly caused by similar organisms as for otitis media such as Pneumococcus (No.1), Hib, or Moraxella. Mucosal edema obstructs the sinus openings (ostia), causing sinus secretions being trapped. Most cases of acute sinusitis are rare complications of the common cold or other URIs. Some cases are caused by nasal obstruction due to foreign body, polyps, or deviated septum. **Sinusitis and rhinitis often coexist--rhinosinusitis.**

**Essentials of diagnosis**

1. **Acute rhinosinusitis**: Based on clinical symptoms and signs-- recent history of an URI followed by nasal stuffiness, purulent nasal discharge, and focal teeth pain; sinus pressure or pain that worsens with percussion or bending head down. Cough and fever may be present in 50% of cases. P/E finds specific sinus tenderness.

2. **Chronic rhinosinusitis**: It may include three subtypes—chronic rhinosinusitis without nasal polyps, with nasal polyps, and allergic fungal rhinosinusitis. Patient usually has a history of recurrent URIs or sinusitis, followed by nasal congestion and postnasal discharge, with mild or absent sinus pain, headache, and fever. Symptoms should be present for > 2-3 months for diagnosis. Patient has increased risk of infection with Staph-aureus and Gram´ rods.

   Sinus CT scan is the preferred means of diagnosis, showing mucosal thickening with or without nasal polyps. Sinus biopsy or culture is more accurate and necessary if symptoms persist after proper antibiotic treatment.

**Treatment**

1. Rhinitis: Treat underlying cause and symptoms.

2. **Acute purulent rhinosinusitis**
   (1) Supportive care—smoking avoidance, saline nasal spray (helps drainage), decongestants (pseudoephedrine or oxymetazoline), and nasal steroid or antihistamines (for allergy).
   (2) Antibiotics—Amoxicillin + clavulanate, TMP-SMX, or levofloxacin is an effective choice.

3. **Chronic rhinosinusitis**
   (1) A brief course of oral prednisone (5 days) plus broad-spectrum antibiotics-- Amoxicillin + clavulanate; or a penicillinase-resistant PCN (oxacillin, nafcillin, etc) for 3-4 weeks.
   (2) Long-term macrolide antibiotic treatment.
   (3) If symptoms persist, refer to an otolaryngologist for a possible endoscopic drainage or surgery.

**Complication**

Mucoceles, nasal polyps, orbital cellulitis (from ethmoid sinusitis), cavernous sinus thrombosis, osteomyelitis, etc.
Septic Dural Sinus Thrombosis and Cavernous Sinus Thrombosis

Dural sinus thrombosis encompasses three basic syndromes: Cavernous sinus thrombosis (CST), lateral sinus thrombosis, and superior sagittal sinus thrombosis. The cavernous sinus is the most frequent dural sinus to become infected and thrombosed as septic CST.

Septic CST is a rare, life-threatening suppurative process of the orbit, nasal sinuses, or central face. The cause is usually from a spreading infection in the nose, sinuses, ears, or teeth. Staph-aureus and Strep are the most commonly associated pathogens, and early antibiotic use is crucial to reduce complications and mortality.

**Essentials of diagnosis**

1. **Fever and orbital pain** after a recent sinusitis or facial infection.
2. **P/E** usually shows orbital edema, exophthalmos, ophthalmoplegia, slowed pupil reactions, and visual deficits. Changes in mental status (confusion, coma) may indicate complicated CNS infection.
3. **Lab diagnosis:** Elevated WBC; 50% of blood cultures are (+); CSF may be (+) with CNS infection. CT and MRI may support diagnosis.

**Treatment**

Take blood for cultures and aggressively treat patient with empiric PCNase-resistant PCN (oxacillin, nafcillin, etc), along with a 3rd or 4th-generation cephalosporin for 3-4 weeks (broad-spectrum coverage). If severe, surgical drainage may be needed.

Pharyngitis (“Sore Throat”) in Adults

It’s mostly caused by viruses (adenovirus, parainfluenza, rhinovirus, and EBV), but Group-A Strep (S. pyogenes) infections (accounting for up to 15%) are more concerned because of the risk of developing rheumatic fever or glomerulonephritis. Other organisms include Chlamydia, Mycoplasma, Gonococci (from oral sex), Corynebacterium diphtheria, and Candida albicans (immunosuppressed patients).

**Essentials of diagnosis**

1. Viral pharyngitis mostly shows fever, cough, and rhinorrhea instead of exudates, except EBV.
2. Sore red throat, tonsillar exudates, tender anterior cervical adenopathy, fever and absence of cough are highly suggestive of Strep pyogenes (Image 22). Mild infections may not show exudates.
3. **Rapid antigen detection test** (RADT) is the best initial testing with high sensitivity and specificity for bacterial pharyngitis. Positive Strep test result means the same as positive throat culture result, whereas a negative Strep test may require a confirmative throat culture if suspicion remains high. A throat culture is the gold-standard (most accurate) test but it takes 24-48 hours to yield results.

**Treatment**

1. Most cases are viral and treated for symptomatic relief instead of antibiotics. Local therapies such as throat sprays and lozenges (with local anesthetics), an NSAID and a short term of glucocorticoids (if severe) may be helpful.
2. If it’s confirmed Strep pharyngitis, oral penicillin V for 10 days is the best treatment. Macrolides and 2nd-generation cephalosporins are alternatives for penicillin allergy. For the rare case of an erythromycin-resistant strain when patient is unable to tolerate beta-lactam agents, clindamycin is an appropriate choice.

3. If it’s mononucleosis, have rest and an NSAID (e.g., ibuprofen).

**Laryngitis**

It is usually caused by viruses, but maybe also by Moraxella catarrhalis and H. influenza. Patient commonly presents with hoarseness, cough, and other URI symptoms. Laryngitis is mostly self-limited and patient only needs symptomatic treatment (similar to that for viral pharyngitis) and voice rest.

*Note:* Shortness of breath, stridor, persistent cough, hemoptysis, throat pain, difficulty swallowing, unilateral otalgia, and weight loss in a patient with voice symptoms raise concern for cancer.

**RESPIRATORY TRACT INFECTIONS**

**The Common Cold**

The “common cold” is the most common upper respiratory tract infection (URI), mostly by a virus. Susceptibility depends on pre-existing antibody level. Rhinovirus accounts for > 50% of cases and have > 100 antigenic serotypes. Thus reinfection with another serotype can cause similar symptoms, since there is no cross-immunity among the serotypes.

**Clinical features, diagnosis, and treatment**

1. Presentations usually include rhinitis (rhinorrhea, nasal congestion), pharyngitis (sore throat), non-productive cough, and malaise. Fever may or may not be present.
2. Most cases resolves in 5-7 days regardless of treatment. Symptomatic and supportive treatment and NSAIDs are adequate therapies in most cases if needed. Avoid abuse of antibiotics.
3. Transmission is mostly by respiratory and hand-to-hand contact. Prolonged infection can lead to secondary bacterial infections such as sinusitis and pneumonia (in immuno-suppressed patient). Best prevention is by regular exercise.

**Influenza (“Flu”)**

It’s a common systemic viral disease caused by influenza A, B, or C (belonging to the orthomyxovirus family) mainly through respiratory droplet nuclei. It’s characterized by strong infectability, rapid transmission, and an epidemic pattern. Influenza can cause damage to the respiratory tract epithelium, leading to complications such as sinusitis, otitis media, bronchitis, and pneumonia. Annual epidemics are due to minor genetic reassortment and usually are not life-threatening except in
immunocompromised and very young or old patients. Rare pandemics are due to major genetic recombination and are often fatal.

**Essentials of diagnosis**

1. Common presentations include systemic symptoms of fever, chills, myalgias, headache, and fatigue, and upper respiratory symptoms of coryza, dry cough, sore throat, and conjunctival injection.

2. Rapid antigen detection of swabs or washings is the best initial test for diagnosis. Viral culture is the most accurate test but it takes a few days to show results.

**Treatment**

1. Effective specific antiviral drugs for both influenza A and B are oseltamivir and zanamivir, and are recommended for all individuals with confirmed or suspected influenza who are severely ill (with dyspnea, tachypnea) or showing signs of rapid deterioration. These antiviral drugs help inhibit the viral replication and spread, and limit the symptomatic duration if used within 48 hours after onset. If it’s > 48 hours, give symptomatic treatment only (acetaminophen, antitussives, etc).

2. All pregnant women with suspected or confirmed influenza should use oseltamivir or zanamivir, even those who present >48 hours after onset provided that they are not yet improving.

3. Amantadine and rimantadine may be cost-effective medicines against influenza A for most influenza cases. Combination therapy with a neuraminidase inhibitor and amantadine may be considered in patients with pneumonia or clinical progression if infection occurs in a region where the isolate is likely to be amantadine-susceptible.

**Prevention**

1. Annual influenza vaccination (IIV, inactivated influenza): Since 2010, it has been recommended to everyone from 6 months of age on. There is also cross-protection against some different strains of virus (including novel viruses). It’s contraindicated in patients with severe allergic reaction (e.g., anaphylaxis) after previous dose or ingestion of egg protein. Benefits: Influenza vaccine has been demonstrated to significantly reduce the disease, hospitalization, and death in numerous studies. It’s especially beneficial to those with high risk.

2. Postexposure prophylaxis: WHO recommends that household contacts of patients with H5N1 avian influenza should receive postexposure prophylaxis with 75 mg of oseltamivir once daily for 7-10 days.

**Bronchitis**

It is an infection or inflammation of the mucous membranes of the bronchial tree and focal parenchyma. Bronchitis can be classified into acute and chronic forms, each of which has unique etiologies, pathologies, and therapies.

**Etiology and classification**
1. **Acute bronchitis**: Over 50% of cases are caused by contagious pathogens, mostly by **viruses** (rhinoviruses, adenoviruses, respiratory syncytial virus, and influenza) and bacteria (Pneumococcus, Hib, etc., similar to those for sinusitis). Others include Mycoplasma, Chlamydia, etc.

2. **Chronic bronchitis**: Mostly due to recurrent injury to the airways caused by inhaled irritants. **Cigarette smoking** is the most common cause, followed by air pollution and occupational exposure to irritants, and cold air. It can lead to **COPD** (chronic obstructive pulmonary disease) and is considered one form of **COPD**.

**Essentials of diagnosis**

1. **Acute bronchitis**: Usually induced by the common cold or influenza, with cough; sputum may or may not be present. Discolored sputum suggests bacterial infection. Systemic symptoms may occur. **P/E** may reveal pulmonary **rales**, but **CXR** is usually **normal**. This confirms the diagnosis and also distinguishes it from pneumonia.

2. **Chronic bronchitis** ("blue bloater"): Presence of a productive cough with “blue” sputum that lasts for > 3 months per year for at least 2 years. **CXR** (Image 11) usually shows thickening of bronchial walls and increased linear markings ("dirty lungs"). The cardiac shadow may be enlarged.

**Treatment**

1. Most acute infections usually do not require antibiotic but symptomatic treatment (NSAIDs) because of the viral nature.

2. More severe cases with suspected bacterial infections are treated initially with amoxicillin +/- doxycycline or TMP-SMZ. If no response, treat with one of amoxicillin-clavulanate, clarithromycin, azithromycin; or with a new fluoroquinolone (gatifloxacin or levofloxacin). Steroids and bronchodilators are usually helpful. For preventive antibiotic use in **chronic bronchitis or COPD**, **azithromycin** is a good choice.

**Pneumonia**

It’s a common infection of the pulmonary tissue characterized by inflammation of the lung parenchyma and abnormal filling of alveoli with fluid (consolidation and exudation). **Pneumonia is a leading cause of death from an infectious disease for patients of all ages.**

**Brief etiologies and drugs of choice -- Important!**

By etiology, pneumonia can be classified as **“Typical” (lobar or bacterial pneumonia, about 50%)** and **“Atypical” (interstitial pneumonia, caused by Mycoplasma, Chlamydia, Legionella, Rickettsia, viruses, or Pneumocystis, etc)**. Predisposing factors include smoking, diabetes, alcoholism, malnutrition, lung cancer, and immunosuppression, etc.

1. **S. Pneumococcus**: It’s the commonest cause of acute community-acquired pneumonia ("lobar pneumonia"). Choose **Macrolides, new quinolones or 3rd-generation cephalosporins**.

2. **Gram’ bacilli** (E. coli, Pseudomonas or Enterobacter): Mostly hospital-acquired or ventilator-associated pneumonia. Choose **3rd-generation cephalosporins** or/and carbapenems.
3. **Staph-aureus**: Usually following viral infection or bronchitis, especially influenza. Choose **semisynthetic penicillins** (oxacillin, nafcillin, etc.).

4. **Hib** (often in smokers, COPD) and **Klebsiella** (often in alcoholics): Choose **2nd/3rd-generation cephalosporins**.

5. **Mycoplasma**: More common in young and healthy patients. Choose **Macrolides**.

6. **Legionella**: A Gram’ bacterium, epidemic infection in older smokers or with special environment such as infected water sources and air-conditioning systems. Choose **Macrolides**.

7. **Pneumocystis carinii (causing PCP)**: Often seen in HIV (+) patients with < 200/uL CD4 cells not on antibiotic prophylaxis. Choose **TMP-SMZ**.

8. **Coxiella burnetii** (Q-fever): From exposure to animals, particularly at the time they are giving birth. Treatment of choice is doxycycline; the second option is erythromycin.

9. **Chlamydia psittaci**: From bird’s feces and upper respiratory secretions. Choose **Macrolides**.

10. **Viruses**: Influenza A or B, adenovirus, parainfluenza virus, RSV, etc. Amantadine is cost-effective for influenza A, and oseltamivir or zanamivir is effective for both influenza A and B.

**Essentials of diagnosis**

1. History of **high fever**, cough, chest pain, tachypnea, and dyspnea (if severe). **Typical, bacterial pneumonia** mostly produces **purulent sputum**; **atypical pneumonia** commonly generates a **nonproductive or “dry” cough**. P/E shows respiratory rate (RR) increase and pulmonary rales.

2. **Lab diagnosis**:

   (1) Leukocytosis with left shift (bandemia); neutrophil dominant for “typical pneumonia” and usually lymphocytosis for “atypical pneumonia”.

   (2) **CXR (Image 12)** is the most important **initial test** to reveal if it’s lobar (bacterial, typically showing lobar consolidation and air bronchograms) or interstitial (other pathogens) pneumonia. The CXR should be considered a sensitive test-- if the findings are not suggestive of pneumonia, do not treat patient with antibiotics.

   (3) **Sputum Gram stain and culture** is the most specific test to diagnose and distinguish the “typical” and “atypical” pneumonia, and thus should be obtained in all patients.

3. **Special pathogens--Lobar pneumonia**:

   Significant purulent sputum indicates **Pneumococcus (“rusty”), Klebsiella (“currant jelly”),** or Hemophilus. P/E usually reveals rales, rhonchi, and signs of **lung consolidation**; tachypnea and dyspnea indicate the severity of pneumonia.

4. **Special pathogens --“Atypical pneumonia”**:

   (1) **Mycoplasma**: Mild nonproductive dry cough and chest pain. Serologic antibody titer is the specific diagnosis if necessary. Usually it’s adequate to make diagnosis on clinical basis and to treat as an outpatient.

   (2) **Legionella**: Nonproductive dry cough, CNS symptoms (confusion, headache, and lethargy) plus GI symptoms (diarrhea and abdominal pain). Specific diagnostic test: Urine antigen test is the initial rapid
tool; other specific tests (take longer time) include specialized culture with charcoal yeast extract and direct fluorescent antibody (Ab) titers. WBC count can be normal or high with left shift.

(3) **Chlamydia-pneumoniae, Chlamydia-psittaci, Coxiella, and Coccidioidomycoses**: All of these are diagnosed with specific antibody titers.

**Treatment**

It depends on the pathogen and severity, inpatients or outpatients. Early empiric treatment is crucial since specific pathogens usually cannot be determined at clinical diagnosis.

1. **Community-acquired pneumonia** -- Empiric treatment against “typical” bacteria and “atypical” pathogens:
   
   (1) **Outpatient**: First choice-- macrolides (erythromycin) cover pneumococcus, mycoplasma, and chlamydia; azithromycin or clarithromycin also covers HIB. Alternatives-- New fluoroquinolones (levofloxacin, moxifloxacin, or gatifloxacin) are also good options.

   (2) **Inpatient**: New Fluoroquinolones (Levo, Moxi, Gati-) or 2nd/3rd generation of cephalosporins (cefuroxime or ceftriaxone) combined with doxycycline or a macrolide or beta-lactam/beta-lactamase combination drug (ampicillin + sulbactam; ticarcillin + clavulanate; piperacillin + tazobactam) combined with doxycycline or a macrolide.

2. **Hospital-acquired pneumonia**: At increased risk of **drug-resistant Gram' bacilli** infection if > 5 days in the hospital, or > age 60, with COPD, DM (diabetes), CVD, renal disease, etc. Give empiric treatment with 3rd-generation cephalosporins (cefazidime or cefotaxime), carbapenems (imipenem), or beta-lactam/beta-lactamase inhibitor Combo (e.g., piperacillin + tazobactam).

3. **Supportive therapies**: **O₂ treatment by degree of severity and hypoxia**: O₂ supply is needed with arterial PO₂ < 70, O₂ saturation < 94% at room air, or RR > 24/min. IV steroids and other medicines in hospital may help patients with serious disease improve further.

**Complications**

1. Pleural effusion: It can occur in about 50% of patients and usually resolve with antibiotic treatment of the pneumonia. Empyema is rare.

2. Acute respiratory failure: It may occur if the pneumonia is severe.

**Preventive pneumococcal vaccination (PCV)**

Two types of pneumococcal vaccines are approved for use in the US:

A. **PPSV23**: includes 23 purified polysaccharide antigens, used in adults; B. **PCV13** (pneumococcal protein-conjugate vaccine): used in infants and children.

1. All children should receive four doses of vaccines (PCV13) --at 2, 4, 6, and 12-15 months of age.

2. Additional vaccination by PPSV23 is recommended for people with increased risk of pneumonia: (1) Age 19-64 with intermediate risk (smoking, chronic heart/lung disease, DM); (2) Patients with serious underlying disease or immunodeficiency [long steroid use, asplenic state, with cancer, or HIV (+)].
PCV13 followed by PPSV23 two months later; (3) All ≥ age 65: PPSV23 alone if vaccinated 5 years ago, or PCV13 followed by PPSV23 6-12 months later.

A single-dose of PPSV23 is enough to confer life-long immunity for most people > 65 y/a. The efficacy of the vaccine is about 70%. Re-dosing in 5 years is only considered for those with severe immunodeficiency.

**Lung Abscess**

It’s necrosis of the pulmonary parenchyma and formation of suppurative cavities (usually > 2 cm) containing necrotic debris or fluid caused by microbial infection.

**Etiology and pathogenesis**

90% of the cases have anaerobes (Peptostreptococcus, Prevotella, Bacteroides), and 50% of them also have mixed aerobes (Strep-milleri, Staph-aureus, E. coli, or Klebsiella) involved. 90% of the cases are closely associated with (assoc/w) pathological aspiration of oropharyngeal contents or foods (with seizures, dysphagia, altered sensorium, etc). The lower lobes are the commonest sites of aspiration in the upright position, and the posterior segment of the right upper lobe is the most common site in the supine position. Noninfectious causes include pulmonary infarction, vasculitis, and cancer.

**Essentials of diagnosis**

1. Symptoms of pulmonary infection (fever, cough, sputum, and chest pain), plus typical putrid, foul-smelling sputum, and a more chronic course (weeks) with weight loss, anemia, and fatigue.

2. Sputum for Gram stain and culture usually will not show the causative anaerobes. A lung biopsy may be necessary for confirmative diagnosis.

3. CXR mostly shows a thick-walled cavity with air-fluid levels. A chest CT scan helps define the exact extent of the cavitation, and differentiate between abscess and empyema.

**Treatment**

1. Hospitalize patient and perform postural drainage.

2. Antibiotic treatment:

   (1) **Clindamycin** is the best empiric medicine for the “above the diaphragm” anaerobes (without confirmed pathogens).

   (2) High-dose amoxicillin + clavulanic acid/sulbactam, or vancomycin is effective against most Gram’ cocci (including MRSA).

   (3) If Gram organisms are suspected, add a fluoroquinolone or ceftazidime.

   (4) Antibiotic therapy should be continued for months until CXR shows significant improvement.

**Pulmonary Tuberculosis (“TB”)**
TB is an infection with Mycobacterium tuberculosis occurring primarily in the lungs. It’s still an important cause of death in many developing countries. About 1/4 of the world’s population has PPD (+) if tested. TB is always spread by person-to-person transmission through respiratory droplets. Bacillus Calmette-Guerin (BCG) vaccination is used in many parts of the world except USA, with 50% +/- effect.

New immigrants occupy > 50% TB cases in the US, and the rest predominantly occurs in people with risky behaviors and factors (alcoholism, healthcare professions, homelessness, chronic diseases, etc). Most of these people have weak T lymphocyte immunity that predisposes them to have TB infection or re-activation.

**Essentials of diagnosis**

1. History of low fever, night sweats, chronic cough, sputum, Wt loss, and an abnormal lung examination. Extrapulmonary TB is < 20% and can affect lymph nodes (LN), GI or GU system.

2. **CXR is the best initial test** for TB, usually showing apical infiltrates, adenopathy, effusion, and chronic cavitations or calcified nodules. **Ghon’s complex**-- a combination of parenchymal lung calcification and hilar lymphadenopathy-- is the pathologic mark of primary TB. It’s more common in children with TB. The combination of a primary focus, TB lymphangitis, and hilar TB lymphadenopathy forms a “dumbbell-shaped” shadow on a CXR film.

3. **Lab tests:**

   (1) Sputum staining for acid-fast bacilli supplies fast and specific diagnosis. Positive staining is the indication of anti-TB treatment, but the low sensitivity requires three negative smears to rule out.

   (2) Sputum culture is the most specific test, but is too slow (taking 4-6 weeks to grow) to guide initial treatment; rather, it is necessary for drug sensitivity testing.

   (3) Special tests for complicated cases: Pleural biopsy is the most sensitive test of pulmonary TB, which will show caseating necrosis. Other tests include examination of thoracic or gastric fluids.

4. **PPD test** (Mantoux test) is used to early screen TB-risky people. The size of the induration (not the erythema) is measured 48-72 h after the injection; > 15 mm is (+). It is not used to diagnose acute TB because it’s neither sensitive nor specific for acute disease.

   (1) PPD (+) indicates history of TB exposure, and the need of CXR. If CXR is also abnormal, it requires three sputum stains for acid-fast bacilli to see if active TB is present. Acid-fast stain (+) indicates active TB and the need for the treatment of four anti-TB drugs (see Treatment below).

   (2) Acid-fast stain (+) with PPD (+) tests but without CXR evidence of active TB indicates the need of 9-month treatment of isoniazid (INH) and Vit-B6 (to prevent peripheral neuritis).

5. **TB in children:** Diagnosis is often based on the presence of the classic triad: (1) recent close contact with an infectious case, (2) a positive TB skin test (TST) or interferon-gamma release assay (IGRA), and (3) suggestive findings on CXR (primary complex) or physical examination.

**Differential diagnosis**

**Pulmonary disease by nontuberculous mycobacteria (NTM, atypical mycobacteria; MAC #1):**
(1) Chronic cough, sputum, malaise, and fatigue usually in an immunodeficient patient; dyspnea, fever, hemoptysis, and weight loss may be present.

(2) CXR shows wide parenchymal infiltrates, often with thin-walled cavities and overlying pleura.

(3) Diagnosis is confirmed by isolation of nontuberculous mycobacteria in a sputum culture.

**Treatment**

1. All TB cases should be **reported to the local health department. All CXR (+) cases** should be **treated with the 4-drugs** (isoniazid, rifampin, pyrazinamide, and ethambutol) for the **first 2 months** (before drug sensitivity results), followed by **INH** (plus Vit-B<sub>6</sub>) and **rifampin** for **another 4-7 months (totally 6-9 months)**. Ethambutol is added if the sensitivity is not known.

2. The TB conditions that definitely **require over 6-month therapy** are: (1) TB meningitis (12 months); (2) TB in **pregnancy** (9 months; avoid pyrazinamide or streptomycin); (3) TB osteomyelitis. (4) TB with HIV (+) (6-9 months). Steroids are helpful in TB meningitis or TB pericarditis.

**Adverse effects (S/E):** All of the TB drugs may have **liver toxicity** except streptomycin (with renal and otic toxicity). INH can also cause peripheral neuritis that can be decreased by Vit-B<sub>6</sub> supply. Rifampin can cause benign bodily fluid coloring to orange/red. Ethambutol may cause optic neuritis. Pyrazinamide can cause a benign hyperuricemia (no treatment).

3. **Treatment of latent TB infection on PPD testing** (9-month treatment of INH + Vit-B<sub>6</sub>, any age):

   (1) **Induration (not erythema) > 5 mm:** Close contacts of active TB patients; abnormal CXR consistent with old, healed TB; steroid use or organ transplantation recipients; HIV (+) persons.

   (2) **Induration > 10 mm:** High-risk groups (patients with immunodeficiency, cancer, DM, or dialysis; healthcare workers, prisoners, recent immigrants, and homeless people).

   (3) **Induration > 15 mm:** Low-risk people and most people.

**Prophylaxis**

*Bacillus Calmette-Guerin (BCG):* It’s not given routinely because the efficacy is uncertain, and only recommended for disseminated TB (such as TB meningitis).

**INFECTIONS OF THE CENTRAL NERVOUS SYSTEM (CNS)**

**Meningitis**

It’s an infection and inflammation of the meninges, the connective tissue that covers the brain and spinal cord. Most causes are infectious and much less ones are non-infectious (such as medications, SLE, sarcoidosis, and carcinomatosis). If the course lasts longer than 4 weeks it’s defined as chronic meningitis and is a complex entity with both infectious and noninfectious causes.

**Etiology – Important!**

1. **Pneumococcus:** #1 common for all patients **beyond the neonatal period.**
2. **Strep-B or E coli**: #1 common in newborns to infants of 6 months in age. *Listeria* and *Klebsiella* are also common for this age group.

3. **Meningococcus**: #1 common in adolescents and spread by respiratory droplets.

4. **Hib**: A very common cause in children in the past but now markedly decreased by the use of the HIB vaccine in children.

5. **Listeria**: More common in immunodeficient (particularly T cells or neutrophil deficiency) or immunocompromised patients—including with steroid use, alcoholism, chemotherapy, leukemia, lymphoma, HIV (+), neonates, the elderly (with lower T-cell function), and pregnancy. However, *pneumococcus* is still the most common pathogen for meningitis with immunodeficiency.


7. **Cryptococcus, Toxoplasma, CMV**: More common in patients with markedly low T cells (as in AIDS, CD4 <100/uL).

**Essentials of diagnosis**

1. Patient may have a history of a local infection (otitis media, sinusitis, mastoiditis, and dental infections), or a systemic infection (endocarditis, pneumonia, etc).

2. Typically presents with high fever, photophobia, headache, nausea, vomiting, confusion, neck stiffness, and positive Kernig and Brudzinski sign.

3. **Rash**: Petechial rash suggests Neisseria (may be fulminant); centripetal spreading rash suggests Rocky Mountain spotted fever; “target” erythema migrans and CN7 palsy suggest Lyme disease; vesicular lesions suggest varicella or HSV infection.

4. **Lab tests**: WBC increase with predominant PMNs and bands. A Lumbar puncture (LP) for CSF biochemistry (protein, glucose, etc), cell count, culture and sensitivity tests are crucial for accurate diagnosis and treatment, but empiric antibiotics (ceftriaxone or cefotaxime) should be started while the results are awaited. Special tests:

   (1) **TB**: Acid fast stain and culture on three high-volume lumbar punctures should be done.

   (2) **Cryptococcus**: Cryptococcal antigen is > 95% sensitive and specific.

   (3) **Lyme and Rickettsia**: Specific serologic tests, ELISA, etc.

   (4) **Virus**: Usually a diagnosis of exclusion.

5. **A head CT is the best initial diagnostic step instead of LP** (which may cause herniation) **if the patient has signs of increased ICP**—vomiting, papilledema, focal motor deficits, or severe confusion. A dose of ceftriaxone prior to the CT scan is recommended (better after a blood sample is taken for culture).

**Table 1-3: CSF Features in Meningitis**

<table>
<thead>
<tr>
<th>Etiology / CSF Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Bacteria</strong>: Pressure &gt; 180 mmH2O, neutrophil increased, protein &gt; 40 mg/dL, glucose &lt; 40 gm/dL.</td>
</tr>
<tr>
<td>2. <strong>Virus, syphilis, rickettsia</strong>: Pressure normal/increased, LC increased, protein and glucose mostly normal.</td>
</tr>
<tr>
<td>3. <strong>TB, fungi (Cryptococcus)</strong>: Pressure &gt; 180 mmH2O, LC increased, protein &gt; 40 mg/dL, but glucose &lt; 40 mg/dL.</td>
</tr>
</tbody>
</table>
Treatment (by etiology)

1. **Bacterial meningitis:** The best empiric treatment is ceftriaxone or cefotaxime against pneumococcus, meningococcus, or Group-B Strep (usually while waiting for CT or CSF results).

2. **Resistant cases:** Vancomycin and corticosteroids are added for severe infection with suspected pneumococcal resistance to PCN, or suspected Staph after neurosurgery.

3. **Immunocompromised patients:** Ampicillin is added to cover Listeria: with very young or old ages, HIV (+), steroid use, pregnancy, or severe cancer.

4. **For special pathogens:**
   (1) Corticosteroid is added to TB meningitis for possible cerebral edema.
   (2) Viral or aseptic meningitis is primarily treated with support.
   (3) Lyme disease with CNS infection is best treated with ceftriaxone.
   (4) Cryptococcus meningitis is treated initially with amphotericin, followed by lifelong fluconazole in HIV (+) patients.

5. **Aseptic meningitis:** It’s mostly self-limited and only needs supportive and symptomatic treatment.

6. **Prophylaxis and vaccination:**
   (1) Respiratory isolation and rifampin or ceftriaxone for all close contacts of patients with meningococcus. General contacts (such as routine school and work contacts) may not be “close contact”.
   (2) MCV (meningococcal vaccine) is now recommended to all children at 11-12 y/a. Add a booster at 16 y/a or in asplenic or immunocompromised patients.

**Encephalitis**

It’s a diffuse inflammation of the brain parenchyma. Encephalitis is often seen with meningitis and is known as meningoencephalitis. Most of the causes are infectious (by viruses).

**Etiology**

**Viruses are the most common cause**, although any bacterial, protozoal, or rickettsial infection can be the etiology. **HSV is the #1 common**; other viruses include varicella, CMV, enteroviruses, and arboviruses (Eastern and Western equine, California and St. Louis, etc; see “PEDIATRICS”).

Noninfectious causes mostly include metabolic encephalopathies and T-cell lymphoma.

**Essentials of diagnosis**

1. Obtain a detailed sexual, travel, and exposure history (to both insects and animals). Patient usually has high fever, headache, altered mental status (confusion, lethargy, or coma), and neurologic deficits (focal deficiency, seizure, or neck stiffness).
2. **Lab tests:** (1) An **LP** for CSF is the crucial test for etiologic diagnosis and differentiations. (2) CSF-PCR is the new efficient test for etiologic diagnosis, with high sensitivity and specificity for HSV, etc. (3) Lymphocytosis (> 5 WBC/uL) with normal glucose is consistent with viral encephalitis or meningitis.

3. A head CT or MRI scan is helpful in differential diagnosis, especially to exclude a focal lesion such as an abscess (usually with confusion and focal neurological deficits), although it may give a non-specific result. **HSV encephalitis usually involves the frontotemporal lobes**, which can be detected by an MRI (increased T2-areas), contrast-CT scan, or EEG (lobal discharges).

**Differential diagnosis**

Patients with **aseptic meningitis** most commonly present with fever and headache with meningismus on examination; may be lethargic but have a normal sensorium. By contrast, patients with **encephalitis** present with mental status changes. Patients with features of both may be considered to have a **meningoencephalitis**.

**Treatment**

**HSV** encephalitis is best treated with **IV acyclovir** for 2-3 weeks. Famciclovir and valacyclovir are also effective but not available for IV route. **Ganciclovir or foscarnet is effective against CMV. Foscarnet** is also used for **acyclovir-resistant** cases. Other treatment is mainly symptomatic and supportive care (for seizures, cerebral edema, etc).

**Brain Abscess**

It’s defined as a focal collection of infected and inflammatory materials within the brain parenchyma, mostly after bacterial infections.

**Etiology**

1. Common pathogens include Strep, Staph, Bacteroides, and Enterobacteria, and are often mixed.

2. Bacteria can spread into the brain from contiguous focal infections such as otitis media, sinusitis, mastoiditis, or dental infections, or cranial trauma/surgery.

3. It may also spread through the bloodstream from endocarditis or pneumonia. Toxoplasmosis can reactivate in patients with severe immunodeficiency or AIDS (when CD4 counts are < 100/uL).

**Essentials of diagnosis**

1. Headache and fever are most common symptoms, followed by focal neurologic deficits and seizures. Note that fever and chills may be absent.

2. CT scan with contrast is the initial test (although CNS malignancy also enhances with contrast). MRI is more accurate than is the CT. A **biopsy** of the lesion with **Gram stain and culture** is the definite means of diagnosis and guide for treatment.

3. In HIV (+) patients, about 90% of brain lesions will be either toxoplasmosis or lymphoma. Thus, CT or MRI (+) is the strong indication of empiric, diagnostic treatment. If the lesion is smaller after 10-14
days of therapies with pyrimethamine and sulfadiazine, then it is diagnostic and this therapy should be
continued.

Treatment

1. Depending on the size of abscess and presence of mass effect, treatment may include IV broad-spectrum antibiotics (> 4 weeks), surgical drainage, and/or steroid.

2. Because the infection is mostly polymicrobial, it is difficult to have an effective monotherapy. Therapies must be guided by the specific pathogens found. Empiric combinations of treatment would be PCN-G (for the Strep), metronidazole (for the anaerobes), and a 3rd-generation of cephalosporin (such as ceftazidine, for Gram' bacilli). Add nafcillin if Staph-aureus is suspected and vancomycin for MRSA.

3. HIV (+) patient is best treated with pyrimethamine and sulfadiazine as a good application for empiric diagnostic therapy against toxoplasmosis for at least 2 weeks.

GASTROINTESTINAL TRACT INFECTIONS

Infectious Diarrhea and Food Poisoning

Most infectious diarrheas are caused by contaminated foods or water by bacteria or their toxins, often overlapped with food poisoning (with more epidemic cases). The best initial test for diagnosis is to look for blood and/or fecal WBCs --viruses, Giardia, Cryptosporidiosis, Bacillus cereus, Staphylococcus are usually negative for it. Common types of infectious diarrhea by pathogens are summarized below.

Table 1-4: Summary of Common Infectious Diarrhea and Food Poinsoning by Etiology

<table>
<thead>
<tr>
<th><strong>Campylobacter jejuni</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sources</strong>: Contaminated food, milk, etc; person-to-person. <strong>Features</strong>: #1 common bacterial diarrhea/coliitis. Fever, headache, severe RLQ abdominal cramps, and diarrhea with blood/pus (50% cases). Occasionally associated with Guillain-Barre syndrome (GBS). Mostly self-limited. <strong>Tx</strong>: Support. If severe, use ciprofloxacin or erythromycin.</td>
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</tbody>
</table>

<table>
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<tr>
<th><strong>Enterotoxigenic E. coli</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sources</strong>: From uncooked food and fecal contamination. It is the #1 common “Traveler’s diarrhea”. <strong>Features</strong>: Abrupt watery diarrhea (rarely bloody); abdominal cramps; rarely vomiting. <strong>Tx</strong>: (1) mostly self-limited, &lt; 3 stools/day: no Tx or use loperamide; (2) If severe, &gt; 3 stools/day: supportive care and ciprofloxacin for 1-3 days.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th><strong>Enterohemolytic E. coli O157:H7</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sources</strong>: From contaminated meat/beef (undercooked) and fruits, etc. <strong>Features</strong>: Abrupt bloody diarrhea, abdominal cramps, looking very sick, possible presentations of hemorrhagic colitis and hemolytic-uremic syndrome (HUS). <strong>Tx</strong>: It’s mostly self-limited; supportive Tx and care for HUS. Antibiotics are not recommended.</td>
</tr>
</tbody>
</table>
Staph-aureus

Sources: Undercooked meat, milk, etc; preformed toxin. Features: Abrupt, intense vomiting about 2-4 hrs after eating; diarrhea is rare. It’s mostly self-limited. Tx: Mostly support is adequate.

Bacillus cereus

Sources: Reheated rice contaminated with Bacillus spores; preformed toxin. Features: Abrupt vomiting 2-4 hrs after eating followed by watery diarrhea later. Tx: It’s mostly self-limited; supportive care or ciprofloxacin.

Shigella

Sources: Transmitted by “4Fs”—“Food, Fingers, Feces, and Flies.” Features: Hours after eating contaminated food, abrupt lower abdominal cramps followed by inflammatory diarrhea with blood and mucus, tenesmus, nausea, vomiting, fever, and even HUS if severe. Tx: TMP/SMX or ciprofloxacin along with supportive care is usually needed. It usually resolves in a week.

Salmonella

Sources: Poultry--raw/undercooked chicken or eggs. Features: High fever, relatively slow pulses, nausea, vomiting, and inflammatory diarrhea; usually self-limited and resolves within a week. Tx: Mainly supportive. Short-term antibiotics may prolong carrier status and increase relapse rate, and thus prolonged antibiotics (ciprofloxacin) should be used if necessary.

Clostridium perfringens and difficile

Sources: C. perfringens--reheated meat; contaminated with spores (unrefrigerated); preformed toxin. C. difficile--usually due to long-term use of broad-band antibiotics. Features: 7-8 hrs after eating, abrupt profuse, watery diarrhea with prominent crampy abdominal pain. Dx: Confirmed by the stool toxin test; WBCs and RBCs in stool. Tx: Metronidazole or vancomycin IV.

Clostridium botulinum

Sources: Honey, canned meat; preformed toxin. Features: Onset in 1-4 days, flaccid paralysis; diarrhea is rare. Tx: Early specific anti-toxin and PCN IV are necessary and effective Tx.

Vibrio cholera

Sources: In endemic areas; toxin-induced illness. Features: Severe, profuse, “rice-water diarrhea.” Tx: Antibiotics and vigorous fluid and electrolyte replacement.

Vibrio parahaemolyticus

Sources: Contaminated seafood. Features: Self-limited abdominal cramp and diarrhea. Tx: Support. If it’s severe with high fever, quinolones should be used.

Yersinia enterocolitica

Sources: Pets; raw/undercooked meat. Features: Often causes sporadic ileitis or ileocolitis—fever and RLQ abdominal pain--similar to appendicitis except for inflammatory diarrhea (+/- blood). It may also mimic ulceric colitis or Crohn disease; associated with high affinity for iron, hemochromatosis, and blood transfusion. Dx: Confirmed by serology and stool culture. Tx: Ciprofloxacin is chosen if severe.


**Giardia lamblia**

**Sources:** Endemic area, food, contaminated mountain water, and immunodeficiency. **Features:** Watery, foul-smelling diarrhea; abdominal bloating. **Dx:** Stool exam for the parasites/eggs, or by bowel biopsy. **Tx:** Oral metronidazole.

**Entamoeba histolytica**

**Sources:** Traveling, homosexual behavior, etc. **Features:** RLQ abdominal cramp and diarrhea with blood or pus, accompanied with mass or obstruction. **Dx:** (1) #1 test is stool culture and oval examination. (2) Serology testing for specific antibodies if necessary. **Tx:** Oral metronidazole.

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## VIRAL HEPATITIS

### Definition and pathogenesis

It’s a group of acute and chronic infections and inflammation of the liver caused by various hepatitis viruses. They are all RNA viruses except HBV, which is a DNA virus. The prevalence is higher in Asian countries. The major **pathogenesis** is virus-induced immunologic inflammation and necrosis of hepatocytes, causing similar manifestations of fever, fatigue, decreased appetite, jaundice (in some), and elevated liver function tests (LFTs). **ALT:AST ratio** is mostly >2, opposite to that in alcoholic hepatitis.

Viral hepatitis is divided into five types: Hepatitis A, B, C, D, and E. **Most clinical cases are hepatitis A and B.** Hepatitis A and E are mainly spread by digestive tract (restaurants and foods) and tend to be self-limited. Hepatitis B and C are mainly spread by blood (transfusion and IV drug abuse) and body fluids and tend to be chronic. A minority of them develop cirrhosis or cancer, particularly hepatitis C with chronic progression. Fulminant hepatic necrosis and failure is rare but can occur with any viral hepatitis and acetaminophen sensitivity. Breast-feeding is not contraindicated for infected mothers because the risk of infant infection is very low.

In serology, **IgM** antibody to hepatitis virus A, C, D, or E indicates acute infection, whereas **IgG antibody** indicates chronic or resolved status. There is no effective treatment for any acute hepatitis. However, effective treatments of chronic hepatitis B and C in recent years have significantly decreased the morbidities of cirrhosis, liver cancer, etc. Liver transplantation is the last resort of treatment for the late-stage hepatic disease or failure.

### Hepatitis A (HA)

HAV is a SS-RNA picornavirus virus, transmitted by fecal-oral route and causes predominantly acute hepatitis. It may also be spread sexually. Poor hygiene or contaminated foods are common risk factors. Incubation period is 15-50 days. After infection, it induces life-long immunity. There is no “chronic hepatitis A.” Risk of fulminant hepatitis is about 1%.

### Essentials of diagnosis
1. General symptoms of fever, fatigue, nausea, jaundice, and elevated LFTs. Anti-HAV IgM (+) indicates a recent or acute exposure.

2. Anti-HAV IgG (+) indicates previous exposure or infection, and life-long immunity. Thus anti-HAV IgG (+) does not distinguish between active disease and immunity. IgM (+) specifies acute infection.

**Treatment:** Most HA resolve spontaneously over a few weeks and only supportive care is needed.

**Prophylaxis**

(1) Inactivated HAV (vaccine) is recommended for infants at 12-15 months by 2-dose series, patients with a chronic liver disease, and for travellers to endemic areas (e.g., a month before going to Asia or Africa), with 95% effectiveness (active immunization). (2) If one will be travelling to endemic areas within 4 weeks, one needs an HAV-IG vaccination (human gamma (γ)-globulin, passive immunization, protective for 2-3 months).

**Hepatitis B (HB)**

Mainly a blood-borne infection caused by HBV—a DNA virus, identified in all body fluids: blood, saliva, synovial fluid, breast milk, ascites, cerebral spinal fluid, etc. Incubation is 1-6 months. About 50% of fulminant hepatitis is caused by HBV. **For acute hepatitis B, 90% of neonate cases will develop chronic hepatitis,** whereas for adults, only 10% will become chronic and 90% will recover. HB is also a major cause of liver carcinoma (hepatoma).

**Essentials of diagnosis**

1. General symptoms of fever, fatigue, nausea, jaundice, and elevated LFTs.

2. HBsAg is present in acute or chronic infection. It is detectable as early as 1-2 weeks after infection. It usually persists in chronic hepatitis (> 6 mo) until the virus is cleared, regardless of symptoms. HBsAg in the acute phase is (+) and soon turns (-) (‘Window period’), followed by anti-HBc IgM (+).

3. Anti-HBs IgG is present after vaccination or after clearance of HBsAg—usually detectable 1-3 months after infection. Anti-HBs IgG (+) alone indicates prior immunity via vaccination; anti-HBs IgG (+) plus anti-HBc IgG (+) denotes a previous infection and immunity.

4. HBeAg (+) is an indicator of active HBV replication and infectivity, following HBsAg shortly.

5. Viral load: HBV DNA is measured by PCR. If it persists for > 6 weeks, chronic HB is likely.

**Table 1-5 Important Serology in HBV Infection**

<table>
<thead>
<tr>
<th>HbsAg</th>
<th>Anti-HBs</th>
<th>Anti-HBc</th>
<th>HbeAg</th>
<th>Anti-HBe</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>IgM +</td>
<td>+</td>
<td>-</td>
<td>Acute HB (Anti-HBc is not protective)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>IgM +</td>
<td>+/-</td>
<td>-</td>
<td>Acute HB, window period</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>IgG +</td>
<td>+</td>
<td>-</td>
<td>Chronic HB, with active viral replication</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>IgG +</td>
<td>-</td>
<td>IgG +</td>
<td>Chronic HB, with low viral replication</td>
</tr>
</tbody>
</table>
**Figure 1-1: Clinical Course and Serology of Hepatitis B Infection** (Courtesy of www.gribbles.com)

- **Treatment**
  1. Acute phase: Supportive therapy is the mainstream of treatment; there is no specific therapy.
  2. **Chronic HB**: 6-12 month treatment with alpha-interferon and lamivudine (3TC) has been proven effective. The goal is to reduce the viral load and convert HBeAg (+) state into anti-HBe (+) state. Adverse effects of alpha-interferon include depression, flu-like symptoms, arthralgia, myalgia, leukopenia, and thrombocytopenia. A similar new drug emtricitabine (FTC) is in clinical study.
  3. Fulminant HB or liver failure: Liver transplantation is the last resort of treatment.

- **Prophylaxis—Important!**
  HBV vaccine (recombinant HBsAg) is the only vaccination that prevents HBV infection and liver carcinoma effectively. Anti-HBe is never seen after the vaccination. It requires a series of three vaccinations for the patient to develop immunity. However, not all patients will have the immunity, and thus testing the titers is necessary.

  **Recommended vaccination:**
  1. Recommended for all children by 3 doses --at birth, 1-2 mo, and 6-18 mo and adults who miss it.
  2. Indicated for people with high risk --healthcare workers and those with chronic liver disease; repeat every 10 yrs if still with risk. The efficiency of protection is about 95% for 10 yrs.
  3. If patient was exposed to HBV (by needle puncture, etc) and received no vaccination before, the patient needs HBIG plus an HBV vaccine within 24 hrs, followed by another two vaccines in a few mo.
  4. If patient has a history of exposure to HBV or previous response—with HbsAb (+) in 9 yrs [even...
with HbsAg (+)], then the patient only needs reassurance.

5. If patient was exposed to HBV and no response to previous vaccinations, then the patient needs HBI G in 24 hrs.

6. If a pregnant patient has HbsAg (+) and HbeAg (+), the infection risk is 95%. The newborn needs HBI G within 12 hrs and the vaccination shortly after delivery, and the patient needs the first HBV vaccination within 24 hrs, followed by another two vaccinations later. Combined immunization not only blocks mother-infant spreading, but also enables the mother’s breast-feeding with HbsAg (+).

**Hepatitis C (HC)**

HCV is spread predominantly by blood products, is the #1 cause of hepatitis among patients with IV drug abuse and blood transfusion, and accounts for 60% of all hepatitis. Sexual transmission is much lower than with HB (less than 5%). Perinatal transmission is 5%. Needle-stick transmission is 5-10%. Incubation is 2 weeks to 6 mo and mostly “silent”, asymptomatic, or with mild symptoms. HCV is rarely acute and it alone rarely leads to severe hepatitis or hepatic failure, which is mostly caused by combined HBV infection. Anti-HCV IgM is not protective in the acute phase. Over 80% of acute HC progresses into chronic hepatitis and is a major cause of cirrhosis (20%) and partial cause of liver cancer. Mnemonic: HC = “4C features”: “Chronic, Cirrhosis, Carcinoma, and Cryoglobulinemia”.

**Hepatitis C-associated extra-hepatic diseases**

Mixed cryoglobulinemia, polyarteritis nodosa, Sjogren syndrome, Hashimoto thyroiditis, membrane glomerulonephritis, ITP, B-cell lymphoma, and plasmacytoma.

**Essentials of diagnosis**

1. Only 25% of cases have above mild symptoms.

2. **Lab tests**: Elevated LFTs. Anti-HCV is usually (+) and indicative of HCV infection, but not protective. Anti-HCV (-) does not rule out infection because this antibody is sometimes not detectable until months after infection. **HCV RNA load by PCR** is the most sensitive and best diagnostic test, usually detectable 1-2 weeks after infection. C4 is decreased.

**Treatment**

1. Most patients are “silent” without symptoms or abnormal LFTs, and thus need no treatment. Follow-up for LFTs is recommended.

2. Symptomatic cases: The effective treatment is long-term use of alpha interferon and ribavirin for 1/2-1 years. If it’s ineffective, new combo medicines ledipasvir/simeprevir-sofosbuvir or ombitasvir-paritaprevir-ritonavir plus dasabuvir are recommended. Treatment can decrease the risk of developing chronic infection and cirrhosis. An HCV vaccine is still under development. Preventive principles are similar to HB.
Hepatitis D (HD)

HDV infects either simultaneously with HBV or as a superinfection with chronic hepatitis B (more severe). HDV is a defective virus, which requires HBV to supply HbsAg for replication. Thus, HDV cannot infect without HBV and the infection carries the highest risk for fulminant hepatitis. HD with HB is predominantly seen in patients exposed to blood products (transfusion, IVDA, etc). Anti-HBs Ab (+) is protective for both hepatitis B and D. Mnemonic: “DDV” feature—“Defective & Dependent Virus”.

Essentials of diagnosis

1. An asymptomatic HBV carrier suddenly presents with severe symptoms of acute hepatitis; or chronic HB worsens abruptly to hepatic failure. Then HBV combined with HDV infection should be suspected.

2. Lab tests: Elevated LFTs; positive serum or liver HDAg or HDV-RNA (indicating superinfection), or positive serum anti-HDV IgM or IgG (high titers) confirm the diagnosis. Anti-HDV may not be present in acute phase, and thus negative result does not rule out infection (repeating is needed). Liver biopsy showing advanced fibrosis supports chronic HD.

Treatment and prophylaxis

There is no specific therapy for acute HD. Same treatment and prophylaxis as for HB may be tried. Foscarnet as an inhibitor of viral DNA polymerases is under clinical trial for fulminant HD.

Hepatitis E (HE)

HE is caused by HEV, which has 4 genotypes and 1 serum type. It can be a co-infected disease among humans and animals. It’s similar to HA, with fecal or oral transmission, no chronic form, and usually self-limited, but it can cause fulminant hepatitis in pregnant patients (20%) with a high mortality. Mnemonic: “Enteric-Fulminant-Maternal” -- “EF-Mom”.

Essentials of diagnosis

1. Most patients have similar symptoms as with HA. It’s more severe with pregnant patients.

2. Lab tests: Elevated LFTs; serum anti-HEV IgM or/and IgG (+), or/and HEV-RNA (+).

Treatment

Same as for HA – most cases resolve over a few weeks and only need supportive care. Prevention with sanitary procedures is recommended.

UROGENITAL INFECTIONS AND SEXUALLY TRANSMITTED DISEASES (STD)

UROGENITAL INFECTIONS
Lower Urinary Tract Infections (Lower UTI)

It’s an infection and inflammation of the urethra (urethritis) or urinary bladder (cystitis, more common). It can be gonococcal and non-gonococcal.

*E. coli* is still the most common pathogen, usually associated with sexual activities in female (more common) and prostate hyperplasia in male. Among patients with multiple sexual partners, *Chlamydia or/and Gonococcus* is most common. Other pathogens include *Staph*-spp., *Klebsiella*, *Proteus*, *Enterococcus*, *Mycoplasma*, *Trichomonas*, and *HSV*. Other risk factors include pregnancy, indwelling urinary catheters, history of UTI, diabetes, and immunocompromised state.

**Essentials of diagnosis**

1. Irritative voiding symptoms—dysuria, urgency, and frequency in urination. Purulent urethral discharge is usually seen with Gonococcus and mucus discharge with Chlamydia. **Fever is typically absent**. P/E may show suprapubic tenderness. Diagnosis of *E. coli* UTI is by clinical impression.

2. Urine dipstick: Nitride (+) indicates Enterobacter (+). Esterase (+) indicates polyleukocytes. RBC may be seen in cystitis.

3. Urine Gram stain showing > 10^5 organisms/mL indicates significant bacteriuria, with 90% sensitivity. With gonorrhea, secretion smear can show the Gram, bean-shaped diplococci inside cells. Culture is the most specific test for gonorrhea.

4. **For Chlamydia**, the new specific methods of testing are polymerase chain reaction (PCR), ligase chain reaction (LCR) on either a genital swab or a urine specimen. Other tests include fluorescent antibody (FA) examination of a direct smear and Chlamydia culture. However, culture sensitivity is low, and thus negative result does not exclude Chlamydia.

**Differential diagnosis**

- **Urethritis and cystitis**: Both have dysuria and urinary frequency and burning, but cystitis does not give urethral discharge.

- **Interstitial cystitis**: (1) Pain with a full bladder or urinary urgency. (2) Submucosal petechiae or ulcers on cystoscopic examination. (3) Diagnosis of exclusion.

**Treatment**

1. For most complicated urethritis and cystitis (by *E. coli*, etc): Oral fluoroquinolone such as ciprofloxacin or levofloxacin for 5 to 10 days is the best therapy. Levofloxacin, ceftriaxone, or ertapenem can be used for resistant organisms.

2. For Gonococcus and Chlamydia: **A single dose of ceftriaxone and azithromycin, or a single dose of ceftriaxone** IM along with 7-day doxycycline PO. Gonorrhea can also be treated with a single dose of ciprofloxacin or cefixime PO.

3. **Same treatment for cervicitis and epididymitis**.
**Pyelonephritis (Upper UTI)**

It’s a diffuse pyogenic infection of the pelvis and parenchyma of the kidney. In adults, it usually ascends from lower UTI and with similar pathogens (*E. coli*, Proteus, Pseudomonas, etc). In children, it is mostly due to bladder-urinary obstruction and recurrence. Recurrences and severe cases may lead to renal scarring, chronic pyelonephritis, emphysematous pyelonephritis, and sepsis (about 10%).

**Essentials of diagnosis**

1. **Fever**, chill, nausea, vomiting, **flank pain plus “irritative voiding symptoms.”**
2. **P/E** demonstrates tenderness on the infected renal site (costovertebral angle).
3. **Lab tests**: Pyuria; urine dipstick-- nitride and esterase (+), WBC cast in urine; RBC may be seen with cystitis. CBC: increased WBC with left shift. Urine cultures: obtain in all suspected cases. Blood cultures: obtain in ill-appearing and hospitalized patients.

**Treatment**

1. Hospitalize patient and take urine or/blood for bacterial culture and sensitivity (C/S) for suspected cases and potential sepsis.
2. Empiric therapies: (1) **Mild to moderate cases**: ceftriaxone, ciprofloxacin or cefepime IV for 7-14 days. (2) **Severe cases with immunocompromise**: ampicillin-sulbactam or ticarcillin-clavulanate or imipenem IV. If no effect in 3 days after changing to proper antibiotics, perform renal ultrasonography or CT/MRI for possible obstruction, abscess, or mass. Treat recurrent cases with antibiotics up to 6 weeks. Repeat urine culture 2-4 days after cessation of antibiotics.

**Prostatitis**

**Bacterial Prostatitis**

It is usually caused by the same Gram` organisms found in UTIs (*E. coli*, etc) **in older men**. In young patients with risky sexual behaviour, Gonococcus and/or Chlamydia are more frequent.

**Clinical features, diagnosis, and treatment**

1. **Acute**: (1) High fever, chill, low back pain, irritative voiding symptoms, and perineal discomfort. (2) **P/E**: Digital rectal exam (DRE) reveals prostate swelling, warmth, tenderness, and induration; urethral discharge is (-). Massage is forbidden for acute infection to avoid spreading to sepsis.
2. **Lab tests**: Urinalysis shows numerous WBCs; urine culture is mostly (+).

   **Treatment**: (1) Hospitalized and monitor for sepsis if with urinary obstruction. (2) **TMP-SMX or ciprofloxacin** (4-6 weeks): with good prostate penetration; if sepsis is suspected, IV ampicillin and gentamycin.

   2. **Chronic**: (1) History of recurrent UTIs with the same organisms; low back pain, testicle pain (epididymitis), irritable voiding symptoms; usually no fever, or tender or inflamed prostate. (2) **Lab tests**: Three sets of urine culture for chronic disease (may be positive for bacterial prostatitis or negative for nonbacterial prostatitis). Prostate secretion by massage gives much higher yields of bacteria than the urine samples.

   **Treatment**: Ciprofloxacin (> 6 weeks) is the No.1 choice of medication. Recurrences are common.
### Table 1-6: Comparison of Prostatitis by Etiology

<table>
<thead>
<tr>
<th>Etiology / Clinical features, diagnosis, and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostatodynia</strong></td>
</tr>
<tr>
<td>Afebrile, irritative voiding symptoms, tender prostate; urinalysis is normal; secretion smear: WBC &lt; 10/HP, culture (-). Dx: Ultrasound and urine cytology are done to rule out tumor/mass for elder patient.</td>
</tr>
<tr>
<td><strong>Non-bacterial</strong></td>
</tr>
<tr>
<td>With similar symptoms but the prostate secretion WBC &gt; 10/HP while bacterial culture is (-). It’s the most common type and more common in younger men. Tx: Sitz baths, NSAIDs, Anti-cholinergics, azithromycin, etc.</td>
</tr>
<tr>
<td><strong>Gonococcal</strong></td>
</tr>
<tr>
<td>History of risky sexual behavior, similar symptoms as above, along with purulent secretion, mid-stream urine WBC &gt; 10/HP, and Gonococcus culture is (+). Prostate massage is forbidden to avoid bacteremia. Tx: Ceftriaxone plus azithromycin (to include Chlamydia).</td>
</tr>
<tr>
<td><strong>Chlamydia</strong></td>
</tr>
<tr>
<td>Similar to symptoms of Gonococcal prostatitis, with mucous secretion but bacterial culture is (-). Positive rate of Chlamydial culture is low, and thus diagnostic Tx is very useful. Tx: Azithromycin +/- Ceftriaxone (for possible Gonococcus).</td>
</tr>
</tbody>
</table>

### Epididymitis

It is the inflammation of the epididymis. Etiology is mostly dependent on age.

#### Clinical features and diagnosis

1. **Acute epididymitis:** (1) Patient typically has fever, irritative voiding symptoms, unilateral testicular pain and tenderness, hydrocele, and palpable swelling of the epididymis ± testicle; usually < 6 weeks. (2) Among sexually active men < 35 y/a, it is mostly caused by C. trachomatis or N. gonorrhea as an STD. (3) In men aged > 35 years, it is more often associated with bacteriuria secondary to obstructive urinary disease, surgery, systemic disease, or immunosuppression. (4) Potential testicular torsion is a surgical emergency.

2. **Chronic epididymitis:** (1) ≥ 6 week’s symptoms of discomfort and/or pain in the scrotum, testicle, or epididymis. (2) It can be subcategorized into inflammatory chronic epididymitis, obstructive chronic epididymitis, and chronic epididymalgia. (3) Chronic infectious epididymitis is most frequently associated with granulomatous reaction (#1 common with TB infection).

3. **Lab tests:** (1) It is rapid, sensitive, specific, and preferred to have Gram stain of urethral secretions demonstrating ≥ 5 WBC per oil immersion field. (2) Gonococcal infection is established by the presence of WBC containing intracellular Gram’ diplococci on urethral Gram stain. (3) Diagnosis is also confirmed by positive leukocyte esterase test on first-void urine or by microscopic examination of it demonstrating ≥ 10 WBC per high power field. (4) Related tests should be suggested for other possible STDs.

#### Treatment
Empiric therapy is indicated before lab results are available. The treatment should target C. trachomatis or N. gonorrhea: (1) Ceftriaxone plus doxycycline are the best for the initial therapy of epididymitis. (2) Additional therapy can include a fluoroquinolone if gonorrhoea is basically excluded. (3) Bed rest, scrotal elevation, and analgesics are recommended until fever and local inflammation have subsided.

SEXUALLY TRANSMITTED DISEASES (STD)

Chlamydia
It is the most common STD. The pathogen is an intracellular organism. The incubation period is 1-3 weeks. Many cases are co-infected with Gonorrhea.

Essentials of diagnosis
1. Approximately 80% in women and 50% in men are asymptomatic.
2. Symptoms in men include dysuria, purulent urethral discharge, scrotal pain & swelling, and fever.
3. Symptoms in women may include dysuria, purulent urethral discharge, and intermenstral or postcoital bleeding.
4. Lab tests: Chlamydial culture is low in sensitivity, and has been replaced by PCR as the most sensitive screening test. ELISA is the most specific diagnostic test. Serologic tests are useless.

Treatment
1. Oral azithromycin one dose or doxycycline for 7 days is effective.
2. All sexual partners should be treated. Asymptomatic, sexually active adolescents should be screened for Chlamydia.

Gonorrhea
It is the #2 common STD caused by Neisseria gonorrhea (a Gram-negative diplococcus). Gonorrhea is usually symptomatic in men but asymptomatic in women, who carry more complications due to delayed treatment. It is almost always transmitted sexually, and many cases are co-infected with Chlamydia.

Essentials of diagnosis
1. Most men have symptoms involving the urethra—dysuria, frequency of urination, purulent discharge, and erythema and edema of the urethral meatus.
2. Most women are asymptomatic. A few cases may show symptoms of cervicitis or urethritis—dysuria, purulent discharge, intermenstral bleeding or dyspareunia.
3. Disseminated Gonorrhea is rare (1-2% and more common in women) and may present with fever, skin rash, arthralgia, migratory/septic arthritis, or even meningitis.
4. **Lab tests:** (1) Gram stain of urethral discharge showing Gram-negative diplococci within WBCs is highly specific for Gonorrhea. (2) Obtain culture in all cases—in men from the urethra and in women from the endocervix. Empiric treatment may be started while culture results are awaited (it takes 1-2 days). (3) Consider testing for suspected syphilis and HIV, and blood culture for disseminated Gonorrhea.

**Treatment**

1. The best therapy is **ceftriaxone** (single dose, IM) to be effectively against Gonococcus and syphilis, **plus azithromycin** (one dose) or doxycycline (for 7 days) to cover coexistent Chlamydia.

2. Other options for Gonococcus include oral cefixime, ciprofloxacin, or ofloxacin. For disseminated cases, patient is hospitalized and treated with ceftriaxone IV for 7 days.

**Syphilis**

It’s a systemic contagious disease caused by a spirochete (Treponema pallidum) through sexual contact, characterized by periods of latency and active manifestations. It can be classified as congenital and acquired syphilis.

**Essentials of diagnosis**

1. **Congenital syphilis:** Infected from the diseased mother at birth. Early disease may be asymptomatic, or with poor feeding and rhinorrhea in infants up to 2 years. Late disease will show Hutchinson teeth, keratitis, scars, and bony abnormality (Saber shins).

2. **Acquired syphilis:**
   
   (1) **Early stage:**

   **Primary syphilis:** Chancre (Image 24)—painless ulcerated papule(s) with clear base and raised borders in genitoanal area (even mouth); **enlarged regional lymph nodes**—painless, rubbery, discrete, and non-tender. It usually appears in 3 weeks and disappears in 3 months,

   **Secondary syphilis** (Images 25-26): Cutaneous rashes (pinkish or pigmented spots) appear in about 2 months, usually symmetric and more marked on the flexor surfaces of the body. LN swellings, papules at mucocutaneous junctions and moist areas (termed **condylomata lata**, extremely contagious), and alopecia are commonly present.

   (2) **Latent stage:** Early latent: < 1 year of infection, asymptomatic, serology (+); may persist for life. Late latent: > 1 year, asymptomatic, serology (+/-); 1/3 of cases may develop late syphilis.

   (3) **Late or tertiary syphilis** (rare now): mostly known as **neurologic syphilis**. It’s rare and characterized by the **Argyll Robertson pupil** (not reacting to light), **Tabes dorsalis** (pain, ataxia, sensory changes, and loss of tendon reflexes), meningovasculitis, and general paresis (memory and personality changes). **Benign tertiary** with symptoms (non-contagious) may develop 10-20 years after the initial infection. The typical lesion is the **gumma**, which is a chronic granuloma that can occur in any organ and heal spontaneously with a scar.

3. **Screening tests** are **VDRL and RPR**; False (+) VDRL can be with TB, EBV, collagen vascular disease, and subacute bacterial endocarditis. All patients should be tested for HIV infection.
4. **Specific tests** are FTA-ABS, MHA-TP, and Darkfield exam of the chancre. They’re confirmative tests for diagnosis.

**Treatment**

1. PCN is the drug of choice for all stages of syphilis. **Primary syphilis** is treated with IM benzathine PCN 2.4 million IU once; **secondary syphilis**: PCN 2.4 million IU once a week for 3 weeks. **S/E:** A reaction called **Jarisch-Herxheimer** can occur in > 50% of patients, with fever, headache, sweating, rigors, and temporary exacerbations 6-12 hours after initial treatment. It’s self-limited and treated with NSAIDs.

2. **Tertiary syphilis** is treated with PCN 10-20 million IU/d IV for 10 days. Patients with severe PCN **allergy** should receive doxycycline (not azithromycin due to resistance) for primary and secondary syphilis, but must be desensitized in tertiary syphilis to use the strong effect of PCN. Pregnant patients must also follow this (be desensitized to use PCN).

**Other Sexually Transmitted Diseases**

They are summarized in Table 1-7.

**Table 1-7: Other Sexually Transmitted Diseases**

<table>
<thead>
<tr>
<th>Lesion / Clinical features, diagnosis, and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molluscum Contagiosum (Image 23)</strong></td>
</tr>
<tr>
<td>1. In young or immunosuppressed patients, HIV (+), etc.; caused by Poxvirus; may or may not be sexually. 2. Single or multiple small, oval, fresh/fleshy, shiny, painless papules on the face, trunk, genital, or extremities. <strong>Dx:</strong> Clinical impression along with KOH smear or Giemsa stain. <strong>Tx:</strong> Cryotherapy, curettage or <a href="#">cantharidin</a> (a topical blistering agent).</td>
</tr>
<tr>
<td><strong>Genital Warts (Image 27)</strong></td>
</tr>
<tr>
<td>1. Also called <a href="#">condylomata acuminata</a>, caused by HPV 6 and 11 (16 &amp; 18 are mostly associated with cervical cancer). 2. Soft, tiny, pink papules (1-5mm) on warm, moist genital surfaces; fast growing and pedunculated (“cauliflower shape”). <strong>Dx:</strong> Clinical features. <strong>Differential Dx:</strong> “condylomata lata”. <strong>Tx:</strong> Cryotherapy, curettage, trichloroacetic acid (TCA), podophyllin, or laser removal.</td>
</tr>
<tr>
<td><strong>Chancroid (Image 28)</strong></td>
</tr>
<tr>
<td>1. Acute STD by <a href="#">H. ducreyi</a> (Gram’ bacillus). 2. Irregular, deep, painful genital papules or ulcerations (about 1cm), and inguinal LN suppuration, with bad odor. <strong>Dx:</strong> Clinical impression plus smear Gram stain; difficult to culture. <strong>Tx:</strong> Any of azithromycin (1dose), ceftriaxone (1dose), erythromycin (7 days), or ciprofloxacin (3 days).</td>
</tr>
<tr>
<td><strong>Genital Herpes (Image 29)</strong></td>
</tr>
<tr>
<td>1. By <a href="#">HSV-2</a>. 2. Red, painful, itching vesicles with circular, scarring ulcers on the genital/perineal areas; enlarged inguinal LN can occur. <strong>Dx:</strong> Tzanck test and culture. <strong>Tx:</strong> Acyclovir, famciclovir, or valacyclovir. It can relapse with repeated sexual contacts.</td>
</tr>
<tr>
<td><strong>Granuloma Inguinale (Donovanosis)</strong></td>
</tr>
</tbody>
</table>
1. **Granulomatis caused by Klebsiella (Calymmatobacterium).** 2. Raised, red, painless papules, with granular ulcerations on the genital or perineum areas; resembles condyloma lata or cancer. **Dx:** Clinical exam with smear/biopsy, or Giemsa/Wright stain (Donovan bodies). **Tx:** Doxycycline for 3 weeks.

**Lymphogranuloma Venereum**

1. By **Chlamydia** trachomatis. 2. Transient, painless, nonindurated, shallow ulcers. 3. Unilateral enlargement of tender inguinal LN; development of multiple purulent draining sinuses, buboes, and scars (“Groove sign”). 4. Fever, dysuria, pelvic/joint pains, and headaches may occur. **Dx:** Clinical features and fluorescent Ab stain for Chlamydia. **Tx:** Doxycycline, TMP-SMZ, or erythromycin.

### Acquired Immunodeficiency Syndrome (AIDS) and Related Infections

AIDS is an acquired immune deficiency syndrome **caused by** the human immunodeficiency virus (HIV). HIV is a retrovirus that particularly targets and destroys CD4+ T-cells, with a subtype HIV-1 (more common) and HIV-2. HIV can be latent for many years and replicates rapidly, progressively decreases the number of CD4 cells, destroys cell-mediated immunity, and increases the risk of developing dangerous opportunistic infections. HIV does not harm patients directly.

**Causes and risk factors**

**IV drug abuse (IVDA) and unprotected sexual intercourse carry the highest risk of developing AIDS.** The risk is 1/100 for each receptive anal intercourse, 1/1000 for vaginal and oral receptive intercourse, and 1/3000-10000 for insertive vaginal intercourse. Other risk factors include blood transfusion, needle sticks (1/300 risk), maternal HIV infection (30% risk without medication), etc.

There is usually a 10-year lag between catching HIV and developing initial symptoms, the time for a normal CD4 level (>700/uL) to the sick level of 200/uL or lower with rapid viral replication.

**Monitoring of the immune system changes**

1. **CD4 T-cell count:** It indicates the degree of immunosuppression, and is the most accurate method of determining what infections or other diseases the patient is risky for, when to start prophylaxis and treatment, and how to adjust them. Without treatment, the CD4 T-cell count drops 50-75 cells per year. **CD4 > 700/uL** is considered normal. **HIV (+) with CD4 < 200/uL or cervical cancer can be diagnosed as AIDS.**

2. **Viral load testing (RT-PCR RNA level):** It is used to (1) diagnose HIV as a sensitive and specific method (especially in babies and patients with undetermined immunoassay); (2) guide antiretroviral therapies, measure response to therapy, and determine the rate of disease progression.

**Table 1-8: Important CD4 Counts and Associated Complications**

<table>
<thead>
<tr>
<th>CD4 (count/uL) / Infections and complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>500-700:</strong> Lymphadenopathy or recurrent <strong>vaginal candidiasis</strong>; no Tx of AIDS is needed yet.</td>
</tr>
</tbody>
</table>
200-500: Oral thrush or vaginal candidiasis, varicella zoster, herpes simplex, pneumococcal pneumonia, pulmonary TB, Kaposi sarcoma, anemia, lymphoma (non-Hodgkin’s), cervical intraepithelial neoplasia (CIN), histoplasmosis, or coccidiodomycosis.

100-200: Pneumocystis carinii pneumonia (PCP) or AIDS dementia complex.

<100: No.1: Toxoplasmosis; No.2: cryptococcus.

<50: CMV, cryptosporidiosis, Mycobacterium avium complex (MAC), progressive multifocal leukoencephalopathy (PML), or CNS lymphoma.

Essentials of diagnosis

1. With the above risk factors for months to years, followed by recurrent viral or fungal infections, ill-defined febrile illness, flu-like symptoms (fever, malaise, rash, LN swelling), night sweats, Wt loss, and cachexia.

2. Lab tests --important!
   (1) HIV screening for risky people -- Third generation EIA or ELISA (enzyme immunoassay) tests detect the presence of HIV-1 or/and HIV-2 antibody as early as three weeks after exposure to the virus. If it’s positive, 1-2 times of Western blot (WB) testing is required for confirmation of HIV-1 or/and HIV-2 Ab (IgG Ab to HIV-1 present 1-2 months after infection). EIA/ELISA has a high sensitivity but moderate specificity for HIV, whereas WB has the highest specificity but moderate sensitivity. A negative EIA/ELISA cannot exclude HIV infection and requires the “fourth generation HIV tests”.

   (2) Fourth generation HIV tests -- The combination antigen-antibody immunoassay is better able to identify acute or early HIV-1/ HIV-2 infection (defined as 6 month period following HIV acquisition), compared with antibody-only (EIA) tests, since they can detect HIV p24 antigen earlier than the antibody. If it is positive, an HIV-1/HIV-2 antibody differentiation immunoassay is performed for confirmation. If the combo-test is negative, the person is considered HIV-negative and no further testing is needed for most patients in whom acute or early HIV infection is unlikely. However, in patients with a negative combo-test but suspected of having acute or early HIV infection, the viral load testing should be performed.

   (3) Viral load testing: A recent HIV load test is considered more sensitive and specificity than EIA/ELISA. Acute or early HIV infection is diagnosed in the presence of a positive virologic test even with a negative immunoassay. However, a viral RNA level <10,000 copies/mL in a patient with a negative serologic test may represent a false positive viral test, as patients with acute or early HIV infection typically have very high levels of viremia. Then the HIV load test should be immediately repeated on a new blood specimen. A second positive viral load test suggests HIV infection, which can be confirmed by a repeat serologic test several weeks later.

   If both the immunoassay and virologic test are negative, it strongly suggests that HIV infection has not been acquired.

   Evaluation needed for HIV (+) persons --important!
   1. Detailed history and physical examination!
   2. Routine chemistry and hematology tests.
3. CD4 lymphocyte count and two plasma RNA tests for HIV load.
4. Screen for syphilis (VDRL/RPR) and PPD test. Syphilis (+) patients with AIDS risk factors should take screening HIV-ELISA. If PPD is (+) (induration > 5 mm), it’s treated with INH for 9 months.
5. Anti-toxoplasma titer test.
6. Hepatitis tests: HAV and HBV serology tests; if (-), vaccination is given. If HAV or HBV antigen is already (+), vaccination is not needed. If both HBV and HCV tests are (+), only HAV vaccine is given.
7. Pneumococcal vaccine (unless CD4 < 200/uL) is given to all HIV (+) children and adults; boosting per 5 years.
8. Mini mental status exam (MMSE).
9. HIV counselling to possibly infected people.

Differential diagnosis

Mononucleosis (due to EBV or CMV), toxoplasmosis, rubella, syphilis, viral hepatitis, disseminated gonococcal infection, and other viral infections.

Treatment

1. Drug resistance testing: For all patients with early HIV infection, drug resistance testing should be performed after the initial diagnosis has been established, regardless of whether treatment is being considered.
2. Most patients: Start antiviral treatment when CD4 < 500/uL with symptoms; for asymptomatic patient, when CD4 < 350/uL, viral load > 55 x 10^3/uL, or opportunistic infection occurs.
   Mediations: Two nucleosides plus a protease inhibitor (Inh). The best initial combination is Atripla -- emtricitabine, tenofovir, and efavirenz. Goal: Viral load < 400/uL.
   (1) Nucleoside reverse transcriptase inhibitors (‘-dine’): Zidovudine (ZDV/AZT), didanosine (DDI), lamivudine (3TC), etc. S/E: Neurologic and pancreatic toxicity, diabetes insipidus.
   (2) Protease inhibitors (‘-avir’): Abacavir, nelfinavir, etc. S/E: GI, liver, and kidney toxicity.
3. Pregnant patients

   All children at birth will carry the maternal HIV antibody and have ELISA (+) testing, but only 25-30% will remain truly infected. Pregnant females with low CD4 or high viral load should be treated fully for their HIV as above (usually AZT plus others). Cesarean delivery for HIV (+) mothers is performed to prevent transmission of the virus if the CD4 is < 350/uL or the viral load is > 1000/uL. Obtain best control of HIV with medications by the time of parturition.
4. Post-exposure prophylaxis

   Indications: All persons with direct exposure to the blood or body fluids of HIV (+) patients.

   Preventive drugs: zidovudine with and without other three combo-drugs for 4 weeks. Statistic data show that zidovudine alone can decrease the risk by 80%.

   Vaccinations: All HIV (+) patients should take vaccines for Pneumococcus, influenza, and HBV.
Opportunistic Infections Complicated by Immunodeficiency or AIDS

Clinical features, diagnosis, and treatment are summarized in Table 1-9.

Table 1-9: Important Opportunistic Infections with Immunodeficiency or AIDS

<table>
<thead>
<tr>
<th>Infection / Clinical features, diagnosis, and treatment</th>
</tr>
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<tbody>
<tr>
<td><strong>Oral and vaginal candidiasis (Image 32)</strong></td>
</tr>
<tr>
<td>Also known as thrush, it appears as white patches of exudates on the tongue, buccal or vaginal mucosa, causing burning pain and itching. It’s caused by Candida albicans mostly in immunocompromised or HIV (+)/AIDS patients. C. albicans is in most cases a normal oral and vaginal microorganism. Dx: Clinical impression. Tx: Simple oral/genital candidiasis can be treated with topical -azole (clotrimazole); severe, complicated candidiasis with immunosuppression or HIV is treated with Oral fluconazole +/- topical -azole for 7-14 days. Sexual partners and asymptomatic patients usually do not need treatment.</td>
</tr>
<tr>
<td><strong>(Oral) hairy leukoplakia (Image 33)</strong></td>
</tr>
<tr>
<td>A whitish, painless patch on the side of the tongue with a corrugated or hairy appearance. It is caused by EB virus and occurs usually in immunocompromised or HIV (+) patients. The white lesion cannot be scraped off. The lesion itself is benign and generally needs no treatment.</td>
</tr>
<tr>
<td><strong>Aspergillosis</strong></td>
</tr>
<tr>
<td>1. A common fungus mostly causing pulmonary diseases by spores in the air only with immunodeficient status. Among many species, fumigatus is the No.1, in rotting organic materials. 2. Asthma-like symptoms: Cough, wheezing, fever, etc. 3. Not invasive type: Mycetoma—“fungal ball”, mainly with hemoptysis. 4. Invasive: More risks with WBC &lt; 500, or cytotoxic drug use. Dx: History, abnormal CXR (“halo sign”), sputum aspergillus culture (+), 45°-angle branching hyphae, skin test (+), elevated eosinophil and IgE. Tx: 1. Allergic: Steroid dosing and asthma drugs, not antifungals. 2. Mycetoma: surgical removal. 3. Antifungals: voriconazole +/- echinocandin first; if intolerant or severe (invasive), amphotericin B or isavuconazole is chosen.</td>
</tr>
<tr>
<td><strong>Blastomycosis</strong></td>
</tr>
<tr>
<td>1. An uncommon fungus in rotting organic material; infected by inhalation. It occurs in both immunodeficient and normal persons; may be endemic to Ohio-Mississippi valleys. 2. Starts with respiratory symptoms (fever, cough, chest pain) and spreads mainly to the skin. Dx: Isolation of the fungus in sputum, pus, or biopsy. Tx: Give prolonged itraconazole/ ketoconazole for mild disease (8 months); amphotericin B for severe disease (8 weeks). Most cases of histoplasmosis need no treatment.</td>
</tr>
<tr>
<td><strong>Coccidioidomycosis</strong></td>
</tr>
<tr>
<td>A pulmonary fungal infection endemic to southwestern U.S. It can present as a flu-like disease or as acute pneumonia, and can also involve extrapulmonary organs. Dx: Confirmed by precipitin antibody increase in IgM (&lt;2 weeks) or IgG (1-3 mo). Tx: Only needed for disseminated disease or in those with a pulmonary disease or immunosuppression. Mild cases are treated with fluconazole or itraconazole. Severe disease is treated with amphotericin B.</td>
</tr>
</tbody>
</table>
PCP (Pneumocystis Carinii Pneumonia)

1. A rare yeast-like fungal infection, found with AIDS when CD4 < 200. 2. Mainly as pneumonia: dry cough, marked dyspnea on exertion, fever, and chest pain. Dx: Bronchoscopy with BCL for direct visualization of the organism; increased LDH. Tx: 1. TMP-SMX 14 days for HIV (-) patients; 2. Atovaquone or pentamidine (with S/E of pancreatitis, hyperglycemia, hypoglycemia) 21 days for HIV infected patients. If failed, clindamycin plus primaquine can be used. Corticosteroids may be added with severe pneumonia. Prophylaxis (when CD4 < 200): oral TMP-SMX is most effective. Dapsone or pentamidine also works.

Toxoplasmosis

1. An intracellular parasite infection around the world. In the U.S., about 50% of the population is antibody (+) but no symptoms. 2. Usually acquired from cat feces and undercooked meat (pork and lamb most). 3. Most symptoms only show with immunodeficient status or AIDS (when CD4 <100): Headache, fever, nausea, vomiting, and neuro/visual deficiency from a CNS mass. Dx: 1. Serology antibody is the #1 method used; direct visualization of the parasite in tissue is the best Dx if available. 2. With AIDS CNS symptoms, contrasted CT or MRI is the best initial test (showing enhanced mass with surrounding edema). Diagnostic Tx (10-14 days) with follow-up scan (seeing shrunk lesions) is also good confirmation. Tx: Pyrimethamine + sulfadiazine is the best (to avoid single-drug recurrence). Leucovorin should be added to prevent pyrimethamine-induced hematologic toxicity. If sulfadiazine is not tolerated, clindamycin can be used.

Cryptococcosis

A rare fungal infection when CD4 <100. Primary infection: meningitis (fever, headache, and neck stiffness). Dx: LP with initial India ink stain and then specific cryptococcal antigen test. A high CSF pressure and antigen titer, and low CSF cell count all imply a worse prognosis. Tx: IV Amphotericin B for 10-14 days, followed by life-long oral fluconazole.

CMV

1. Infected with AIDS when CD4 < 50. 2. Mainly presenting as retinitis (painful eyes and blurry vision); sometimes with colitis (diarrhea). Dx: Funduscopy for retinitis; colonoscopy with biopsy for colitis. Tx: Ganciclovir (S/E: neutropenia); foscarnet or cidofovir (S/E: renal toxicity).

MAC (Mycobacterium avium complex)

1. A rare non-TB mycobacterium infection with AIDS when CD4 < 50. 2. Major manifestations: Chronic cough, sputum, fever, bacteremia, wasting, and anemia. Dx: Sputum or blood culture for mycobacteria. CXR helps show spreading parenchymal infiltrates. Tx: Standard regimen-- clarithromycin, rifabutin and ethambutol. Prophylaxis: When CD4 < 100, oral clarithromycin, rifabutin, or azithromycin; stop when CD4 > 100 for a few mo.

Cryptosporidiosis

1. A rare spore-forming protozoa infection with immunodeficiency when CD4 < 50; contracted by fecal-oral route. 2. Typically with severe watery diarrhea. Dx: Stool analysis shows oocytes. Tx: Supportive care for most cases; nitazoxanide for persistent cryptosporidial infection.

HHV8—Kaposi Sarcoma (KS):
BLOOD INFECTIONS AND RELATED DISEASES

Sepsis

Sepsis is a systemic inflammatory response syndrome (SIRS) caused by overwhelming bacterial infections and their toxins in the blood stream. Septic shock is defined as sepsis-induced hypotension and organ dysfunction due to poor circulatory perfusion. Multiple organ dysfunction syndrome (MODS) refers to progressive organ dysfunction at the severe end of SIRS.

Etiology

1. Gram- bacterial shock: Usually secondary to vasodilatation caused by endotoxins (lipopolysaccharide) from E. coli, Pseudomonas, Klebsiella, or Proteus, etc. Elderly patients are more often affected.
2. Gram+ bacterial shock: Usually secondary to fluid loss caused by exotoxins from Staph, Strep, etc. All adults can be affected.
3. Neonates: Group-B Strep, E. coli, Listeria and HIB are the most common pathogens.
4. Children and asplenic patients: Encapsulated bacteria (Pneumococcus, Klebsiella, HIB, Meningococcus) are the most common pathogens.
5. IV drug abuse (IVDA) and indwelling lines: Staph-aureus and Staph-spp. are the most common organisms.

Essentials of diagnosis

1. Usually with a history of bacterial infection followed by an abrupt onset of fever, chills, tachycardia, tachypnea, and altered mental status.
2. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, which may be defined as infusion of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). Early-stage shock is mostly “warm shock” with warm skin and extremities. Late-stage often shows “cold shock” (T<36°C), with hypotension and cool skin and extremities, indicating severe disease. Petechiae or ecchymoses suggest DIC (Image 34).
3. Lab tests: Leukocytosis (WBC > 12,000/uL) or leukopenia (WBC < 4,000/uL) with increased bands, decreased platelets (< 100,000/uL in 50% of cases), elevated LFTs and creatinine, and hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes. Cultures of the blood, sputum, or urine may be (+). CXR may show lung infiltrates. If DIC is suspected, coagulation tests should be performed, which may show coagulopathy (INR >1.5). Diagnosis is by clinical experience.

Treatment

1. The mainstreams of therapy include securing the airway, correcting hypoxemia, administering aggressive IV fluid, vessel-active agents, empiric antibiotics, surgical drainage of infected fluid
collections, removal of infected lines or catheters, and appropriate support for organ dysfunction. The main goal is to maintain BP and perfusion to end organs.

1. For initial fluid replacement, administer a crystalloid (rather than hyperoncotic) solution by early goal-directed therapy.

2. For patients who remain hypotensive following intravascular volume repletion, give vasopressors (norepinephrine).

3. For patients with severe sepsis and septic shock that are refractory to intravenous fluid and vasopressor therapy, additional therapies, such as inotropes, glucocorticoids and blood transfusions (when Hb < 7 g/dL), are administered based on individual assessment.

4. Antimicrobial regimen: Strong and adequate antibiotics should be administered within the first 6 hours after blood sample is taken for culture and sensitivity testing. Special invasive bacteria such as MRSA and Pseudomonas should be considered.

2. Supportive treatment includes mechanical ventilation in pulmonary dysfunction, hemodialysis in kidney failure, transfusion of blood products, and drug and fluid therapy for circulatory failure. ICU admission may be necessary. Glucocorticoid therapy, nutritional support, and glucose control are beneficial in severe sepsis. Ensuring adequate nutrition is crucial during prolonged illness.

**Toxic Shock Syndrome (TSS)**

Staph-aureus strains produce exotoxins that lead to three syndromes: food poisoning (caused by ingestion of S. aureus enterotoxin), scalded skin syndrome (caused by exfoliative toxin), and toxic shock syndrome (TSS) --caused by toxic shock syndrome toxin-1 (TSST-1) and other enterotoxins. TSS is characterized by shock and multi-organ dysfunctions mainly due to the TSS toxin rather than the bacteria. It’s usually contracted by the use of tampons or sponges during menstruations, or by infected wounds, burns, or insect bites. A minority of cases are caused by Streptococcus.

**Essentials of diagnosis**

1. Typical toxic shock manifestations include fever, headache, tachycardia, hypotension, mucosal changes (“strawberry tongue”), desquamative rash on palms and soles, and GI symptoms (nausea, vomiting, diarrhea). Muscular, renal and hepatic dysfunctions and hypo-Ca can also occur.

2. Lab tests: CBC usually reveals leukocytosis with predominant neutrophils. BUN/creatine may be increased. Diagnosis is on clinical basis. Confirmative diagnosis is by isolation of Staph-aureus from vaginal secretion or Strep from oral swab. Blood culture is mostly (-).

**Treatment**

1. Supportive: Stabilize patient by correction of hypovolemic shock (with aggressive fluids) and removal of toxin and infected material and tissue.

2. (1) For suspected MRSA, **clindamycin plus vancomycin** is the best empiric etiologic therapy.
(2) If culture shows methicillin-susceptible S. aureus, clindamycin plus oxacillin/nafcillin is the best.
**Infectious Mononucleosis (IM)**

It’s a systemic mononucleosis due to **E-B virus (EBV)** infection, mostly transmitted through close contact with body fluid (like saliva). It’s also known as the “Kissing disease”, more common among young adults. Most adults (90%) have been infected with EBV and are carriers. One infection typically induces lifelong immunity. The incubation period is usually 2-5 weeks.

**Essentials of diagnosis**

1. Most patients present with high fever (up to 40°C), pharyngitis, enlarged tonsils with exudate, palatal petechiae, cervical lymph node swelling with tenderness; some with bilateral eyelid edema, a generalized maculopapular rash, and hepatosplenomegaly. Up to 30% of cases may be misdiagnosed carriers of Group-A Strep.

2. **Lab tests:** Lymphocytosis and increased circulating atypical T cells along with a positive **Monospot heterophile antibody test support diagnosis** in most cases. Monospot test may be negative in the first few weeks. Measurement of EBV-specific antibodies is usually not necessary since the vast majority of patients are heterophile positive (relatively specific). However, testing for EBV-specific antibodies (IgG and IgM VCA) may be warranted in patients with suspected IM who have a negative heterophile test. Specific IgG and IgM EBV-CA (-) or IgG EBNA (+) excludes acute primary EBV infection. Mild thrombocytopenia and elevation of hepatic enzymes may exist.

3. **Special notes:** (1) Ampicillin use during EBV infection can cause a prolonged, pruritic maculopapular rash, which is not associated with over-sensitivity to beta-lactams and will remit after ampicillin is stopped. (2) CMV may cause an IM with negative results of Monospot and EBV antibody tests.

**Differential diagnosis**

Infections by Group-A Strep, CMV, HHV-6, or HIV, etc.

**Treatment**

1. Most therapies are **supportive and symptomatic**. There is no effective treatment against EBV. Avoid strenuous activities until splenomegaly resolves to prevent splenic rupture.

2. In case of airway obstruction (by swollen tonsils), severe autoimmune hemolytic anemia, or thrombocytopenia, IV steroid is indicated (but not for most cases).

**Complications**

Group-A Strep pharyngitis (#1, 10%), upper airway obstruction, autoimmune hemolytic anemia, CNS infection (aseptic meningitis, encephalitis, CN palsies, neuritis, etc), splenic rupture (< 0.5%), and fulminant hepatitis (rare).

**Fever of Unknown Origin (FUO)**

It refers to a condition in which the patient has an elevated temperature but despite investigations by a physician no explanation has been found. The present criteria are:

1. Fever higher than 38.3°C (101°F) on several occasions;
(2) Persisting without diagnosis for at least 3 weeks;
(3) At least 1 week’s evaluation in hospital (or 3 outpatient visits and 3 day’s hospitalization).

**Etiology**

In adults, **infections and cancer account for > 60% of cases of FUO**, while autoimmune diseases account for about 15%.

1. **Infections**—the most common cause: TB, occult abscesses, UTI, endocarditis, sinusitis, infectious mononucleosis, HIV, malaria, etc.
2. **Occult neoplasms**—#2 common: lymphoma, leukemia, hepatic and renal cell carcinoma, etc.
3. Autoimmune diseases—SLE, Still disease, vasculitis, etc.
4. Others—granulomatous disease, pulmonary embolism, hemolytic anemia, hepatitis, gout, subacute thyroiditis, drug fevers, factitious disorder, etc.

**Essentials of diagnosis**

1. A detailed history of travel, animal exposure, immunosuppression, drugs and toxins is important.
2. Patient often presents with fever, chills, headache, myalgias, night sweats, and malaise.
3. Confirm the fever and perform the following minimum lab tests:
   (1) CBC with differentiation, ESR or C-reactive protein;
   (2) Three routine blood cultures drawn from different sites over a period of at least several hours without antibiotic use
   (3) Serum LDH and CPK;
   (4) Rheumatoid factor and antinuclear antibodies;
   (5) Heterophile antibody test in children and young adults;
   (6) Tuberculin skin test (PPD) or interferon-gamma release assay;
   (7) HIV antibody assay and HIV viral load for patients at high risk;
   (8) Serum protein electrophoresis
   (9) CXR; PET scan; CT scans of chest and abdomen +/- laparoscopy or colonoscopy.

   Additional: invasive procedures—biopsy of lymph nodes, bone marrow, or other tissues for suspected tumor or abscess may be necessary to make a diagnosis.

4. Sometimes the cause is determined by observation and excluding all less possible ones. However, undiagnosed cases can be 30-50%. Most adults who remain undiagnosed have a good prognosis. Most children with FUO have treatable or self-limited diseases, with more likelihood of etiologic diagnosis.

**Treatment**

Try to target the most likely cause. Stop unnecessary medicines. Empirical treatment with NSAIDs or antibiotics should generally be avoided as diagnostic measures in children with FUO. Exceptions include NSAIDs in children with presumed juvenile idiopathic arthritis and ant-TB drugs in critically ill children.
with possible disseminated TB. Empirical trials of broad-spectrum antibiotics can mask or delay the diagnosis of important infections, such as meningitis, infectious endocarditis, or osteomyelitis.

**BONE, JOINT AND MUSCLE INFECTIONS**

**(Pyogenic) Osteomyelitis**

It’s defined as an infection and inflammation of any portion of the bone, including marrow, cortex, and periosteum. It can be acute hematogenous (septic) osteomyelitis, or secondary to chronic infection, decubitus ulcer, trauma, or vascular disease in elder patients.

**Etiology--similar to sepsis**

1. **Hematogenous osteomyelitis:** Injection drug users, sickle cell disease, children and the elderly, mostly in the long bones of the lower extremities.

2. **Osteomyelitis from a continuous focal infection:** Prosthetic joint replacement, decubitus ulcer, neurosurgery, and trauma.

3. **Osteomyelitis associated with vascular insufficiency:** Patients with diabetes and vascular insufficiency are susceptible to it.

**Associated specific microorganisms**

1. **Staph-aureus** is still the #1 common microorganism in most cases.

2. **Salmonella** is more common in osteomyelitis with sickle cell disease (SCD).

3. **Pseudomonas** is more common with IV drug abuse, foot puncture, or chronic osteomyelitis.

4. **Staph-epidermidis** is more common with hip replacement.

**Essentials of diagnosis**

1. Fever, fatigue, localized bone pain, erythema, swelling, and tenderness over the infected bone, usually from hematogenous causes. With a vascular disease, an overlying ulcer or wound/sinus is usually seen. A draining sinus tract through the skin may form in chronic disease.

2. The **earliest sensitive tests are the technetium (T\textsuperscript{99})** bone scan (moderately specific) and **MRI (highly specific, especially for diabetic and vertebral osteomyelitis)**. Plain X-ray is usually negative early in the course and later may show periosteal elevation with limited sensitivity. Lab tests usually show leukocytosis, elevated ESR and/or C-reactive protein (CRP). Blood culture and bone biopsy for culture may be needed to guide therapy.

3. **Bone biopsy for culture:** It’s the most accurate test to guide treatment but is invasive. ESR is increased significantly and non-specifically, and only used for follow-ups after treatment. WBC counts may or may not be elevated and not very helpful in diagnosis.

**Treatment**
1. **Empiric treatment of Staph-aureus** by Oxacillin or nafcillin plus an aminoglycoside or a 3rd-generation cephalosporin (for Gram’ organisms) for 4-6 weeks for acute osteomyelitis is the best initial therapy until the specific pathogen is isolated. Vancomycin is best for MRSA and coagulase-negative Staph. Cefepime is best for Pseudomonas.

2. Chronic osteomyelitis must be treated with specific IV antibiotics for 12 weeks, followed by another 8-12 weeks orally.

3. Surgical debridement of necrotic bone is an important part of treatment.

**Infectious Arthritis**

It’s also known as **septic arthritis**, a bacterial infection of the joint, and generally divided into **Gonococcal and non-gonococcal arthritis**. Gonococcal arthritis is mostly in young patient and with a history and symptoms of an STD. **Non-gonococcal** arthritis is mostly caused by Staph-aureus in elder patient and with a history of a joint lesion (gout, rheumatoid, or osteoarthritis), artificial joint, previous surgery, IV drug abuse, or Sickle cell disease (SCD).

**Essentials of diagnosis**

1. **Gonococcal arthritis**: Prodromal migratory polyarthralgias and tenosynovitis are most common, along with characteristic petechiae or purpura on the skin and purulent monarthritis (in 50% of cases). It is most common in young women during menses or pregnancy. Symptoms of urethritis are frequently absent. **Gonococcus is difficult to culture**, with only 50% (+) from joint aspirates and < 10% (+) from blood cultures; other sites (cervix, urethra) often have higher positive rate of culture. Aspirate WBC count is usually > 60-70 x 10^3/uL (mostly PMNs).

2. **Non-gonococcal**: Acute onset of inflammatory monoarticular arthritis, mostly in weight-bearing joints and wrists (knee as #1), with a swollen, erythematous joint with tenderness and a decreased range of motion. Skin rash is rare. Previous joint damage or drug injection is a risk factor. Infection with causative organisms is commonly found elsewhere in the body. **Joint aspirate assay**: usually yields a large volume of effusions, with WBC counts mostly > 50 x 10^3/uL (mostly PMNs) and a low glucose concentration; synovial **bacterial culture has > 90% (+) rate**, and Gram stain is 50% (+).

**Treatment**

1. If the initial Gram stain of the synovial fluid shows **gram-positive cocci, nafcillin/oxacillin plus gentamicin** (to cover most Staph and Strep) or **vancomycin** (to cover possible MRSA and severe infections) should be started.

2. If the initial Gram stain of the synovial fluid shows **gram-positive bacilli**, a 3rd-generation cephalosporin (ceftriaxone, cefotaxime, or ceftazidime) is started. If **Pseudomonas is suspected**, ceftazidime plus gentamicin should be given.

3. **If Gonococcus is suspected**, ceftriaxone is the best medication—patient has dramatic response.

4. Drainage: (1) Daily aspiration of affected joint is necessary until effusion disappears. (2) Surgical drainage may be needed if response to antibiotics is poor, or if the hip or shoulder joint is infected or any joint damage is involved.
**Gas Gangrene (Clostridial Myonecrosis)**

It is the necrotizing destruction of muscle by gas-producing anaerobic organisms (#1 is *Clostridium perfringens*), producing signs of sepsis. It develops either contiguously from an area of deep trauma/surgical injury (usually due to *C. perfringens*) or hematogenously from the gastrointestinal tract with muscle seeding (usually due to *C. septicum*). It’s more of a concern during times of war.

**Essentials of diagnosis**

1. Pain, swelling and edema at the wound site start within 1-4 days of incubation, often followed by fever, hypotension, and tachycardia. Focal crepitation and renal failure are late-stage signs.

2. **Lab tests:** A Gram stain of the wound shows Gram+ rods without WBC. Culture for *C. perfringens* may be (+) but not highly sensitive. Gas bubbles on an x-ray are suggestive of this disease, but it may also be caused by *Strep*. **Direct vision** of pale, dead muscle with a brownish, sweet-smelling discharge is **highly suggestive of the diagnosis**. **Definitive diagnosis** requires demonstration of large, gram-variable rods at the site of injury. Histopathology demonstrates characteristic **absence of acute inflammatory cells**. Gas in the soft tissue may be observed at the bedside and/or radiographically.

**Treatment**

The main therapy is **high-dose PCN** (24 million IU/day) **plus clindamycin** (especially if allergic to PCN) IV early against *C. perfringens*, followed by surgical **debridement** or amputation. Hyperbaric O₂ therapy may be helpful with the above treatment, but may not always be beneficial.

**Tetanus**

It’s a severe infectious complication of wounds caused by neurotoxins of *Clostridium tetani*, a Gram+ anaerobic rod with spore. It usually takes 1-7 days to develop. The neurotoxin is an exotoxin, which can block inhibitory transmitters at the neuromuscular junction and cause extensive muscle spasms.

**Essentials of diagnosis**

1. History of a deep, dirty wound 1-7 days ago, followed by tonic spasms of voluntary muscles — first by masseter muscles causing **typical “trismus or lockjaw”**, then stiff neck, arm flexion, leg/foot extension, dysphagia, headache, irritability, and eventual respiratory arrest. It carries a high mortality rate.

2. Early diagnosis by clinical experience and immediate treatment are crucial to save life. Wound cultures can be obtained but may not be a reliable means of diagnosis.

**Treatment**

1. Immediate admit patient to the ICU and provide possible airway and respiratory support. Recommended therapies include IV specific antitoxin IG (to neutralize the unbound tetanus toxin), large doses of PCN (10-14 days) or metronidazole (7-10 days) against *C. tetani*, control of muscle spasms with neuromuscular blocking agents, and thorough wound debridement to eradicate spores and necrotic tissue.
2. Prophylaxis: (1) Tetanus toxoid plus IV IG for patients with any suspected dirty wound beyond 5 years of vaccination. (2) DTaP is recommended at birth, 2 mo, 4 mo, 6 mo, 15-18 mo, and 4-6 y/a. Tetanus toxoid should be boosted every 10 years.

**ARTHROPOD-BORNE AND ZOONOTIC INFECTIONS**

**Lyme Disease**

It is an arthropod-borne infection spread by *spirochete Borrelia burgdorferi* from a small (deer) tick bite (Ixodes scapularis, usually in summer), endemic to the Northeast and Midwest of the US. It’s characterized by a fever and a rash, and can recur as arthritis, cardiac disease, or neurological disease if untreated. “Post-Lyme disease syndrome” refers to the nonspecific symptoms (such as headache, fatigue, and arthralgias) that may persist for months after treatment of Lyme disease.

**Essentials of diagnosis**

There are three clinical stages:

1. **Early localized infection**--erythema chronicum migrans (Image 35): Circular and expanding, begins 3-30 days after the tick bite; the rash usually resolves in a few weeks without treatment.

2. Early disseminated infection: 50% of patients have flu-like symptoms, enlarged LN, migratory joint pain, meningitis, encephalitis, cranial neuritis (often bilateral facial nerve palsy), and cardiac lesion (A-V block, myocarditis, pericarditis).

3. Late persistent infection: Arthritis, chronic polyneuropathy (shooting pains, numbness) or encephalomyelitis (memory, mood changes, psychosis), acrodermatitis chronica atrophicans (rare), etc.

4. **Lab tests**: Typical rash with a fever may not need confirmatory testing. ELISA for IgM (early) and IgG followed by a Western Blot (confirmation) is the standard diagnostic method. A (-) result does not necessarily rule out recent infection. Receiving blood transfusion in recent months may cause false (+).

**Treatment**

1. Asymptomatic cases may not need treatment, or only need a prophylactic dose of doxycycline with special concerns (e.g. a clear tick bite, endemic area). Limited Lyme disease is treated with oral doxycycline or amoxicillin (with pregnancy).

2. Severe cases and complications (with neurological manifestations, 3rd-grade heart block, arthritis, myocarditis, or encephalitis) are treated with IV ceftriaxone for at least 30 days.

**Rocky Mountain Spotted Fever (RMSF)**

It’s a small-vessel vasculitis caused by R. rickettsii transmitted by the dog/wood tick. It is usually in summer and endemic to the Mideast to Midwest of the US.

**Essentials of diagnosis**
1. **Typical triad -- abrupt fever, headache, and rash** (from hands or feet spreading centripetally). Initial diagnosis can be made based on this typical triad in an epidemic area.

2. Other symptoms include confusion, lethargy, dizziness, irritability, neck stiffness, and GI upset. Patient may die of a severe complication such as heart failure (from myocarditis), pulmonary edema, or CNS hemorrhage or edema.

3. **Lab tests**: Thrombocytopenia, hypo-Na, and elevated LFTs are common. Direct immunofluorescence testing or immunoperoxidase staining for R. rickettsiae in skin biopsy makes a timely diagnosis. Indirect fluorescent antibody (IFA) testing makes a retrospective, specific diagnosis, usually at the 2nd week.

**Treatment**

1. Oral **doxycycline** is given for 7 days or more than 3 days after defervescence. Administer by IV route if vomiting is present.

2. **Chloramphenicol** is given for patients with CNS complications or pregnancy.

**Malaria**

It’s a protozoal disease caused by four strains of the genus Plasmodium (P. falciparum, P. vivax, P. ovale, and P. malaria), and transmitted by a female Anopheles mosquito. Among the four strains, **P. falciparum** has the highest morbidity and mortality. Although malaria has been largely eliminated in North America and Europe, it’s still endemic in certain areas in Africa and Asia. Thus, chemoprophylaxis and mosquito protection should be used for travellers to the endemic areas.

**Essentials of diagnosis**

1. History of exposure in an endemic area, with typical periodic attacks of **sequential chills, high fever (> 41°C), and sweating** over 4-5 hours. Other symptoms include headache, dizziness, malaise, GI upset, myalgias, and arthralgia. Some symptoms may recur every 2-3 days.

2. **P/E** usually finds **splenomegaly**, rash, and LN swelling 4-5 days after symptoms. If CNS is infected, confusion, neck stiffness, and neurologic signs may be found.

3. **Lab tests**: CBC mostly reveals hemolysis-like anemia with reticulocytosis, and low to normal WBC. Giemsa/Wright-stained blood films (thick and thin) are sent for specific diagnosis by experts. Specimens are collected at 8-hour intervals for 3 days, and during and between febrile periods.

**Treatment**

1. Uncomplicated cases are treated with oral chloroquine or mefloquine. If chloroquine/mefloquine resistance is suspected as in many countries, **artemether + lumefantrine/amodiaquine** or quinine plus tetracycline can be used.

2. P. vivax and P. ovale strains are usually resistant to chloroquine, and thus primaquine is added to eradicate the hypnozoites in the liver.
3. **Severe**, complicated cases or *P. falciparum* infection are treated by **rectal and IV artesunate** or IV **quinine** (with more S/E), followed by doxycycline. Symptomatic and supportive therapies are also important. For a pregnant patient, doxycycline is replaced by clindamycin.

4. **Prophylaxis** is recommended to travellers to endemic regions. Atovaquone-proguanil or mefloquine is the agent of choice because it also covers chloroquine-resistant cases.

**Complications**

Cerebral malaria, severe hemolytic anemia (mostly by *P. falciparum*), acute tubular necrosis and renal failure (“Blackwater fever”), pulmonary edema, bacteremia, and DIC.

**Rabies**

It is a rare devastating, deadly viral encephalitis caused by bites or scratches by infected animals (#1 is **raccoon**, followed by bat or dog). Rabies is only occasionally found in developing countries where rabies vaccination of animals is not widespread. The incubation period ranges from 30-90 days and varies. **Once symptoms appear, it is always fatal!**

**Essentials of diagnosis**

1. History of a bite by a rabies-suspected animal followed by typical symptoms -- sore throat, headache, nausea, vomiting, fever; encephalitis (confusion, combativeness, hyperactivity, seizure); **hydrophobia** (inability to drink, laryngeal spasm with drinking, hypersalivation—“foaming at mouth”); almost **always progresses to coma and death**.

2. **Lab diagnosis**: (1) Virus isolated in infected tissue and saliva. (2) 4-fold increase in serum antibody titers. (3) Negri bodies identified in histology. (4) PCR detection of virus RNA.

**Treatment and prophylaxis**

Rabies is an invariably fatal viral disease that can be prevented with proper wound care and postexposure prophylaxis. Ketamine and midazolam may be helpful in symptomatic control. Amantadine may be used for its potential antiviral activity.

1. Clean the wound thoroughly with soap and be ready for life support care.

2. For a wild animal bite (raccoon, bat, or dog), the animal should be captured at best efforts and killed for immunoassay of the brain.

3. For a home dog or cat bite in an endemic area, the animal should be captured and observed for 10 days. The animal most likely does not have rabies if its conditions remain the same.

4. For a known rabies exposure, both passive and active vaccinations should be given: passive—IV human rabies IG to the patient; active—3 doses of antirabies vaccine IM over a 28-day period.
## Other Arthropod-Borne and Zoonotic Diseases

These are summarized in Table 1-10 below.

### Table 1-10: Summary of Other Arthropod-Borne and Zoonotic Diseases

<table>
<thead>
<tr>
<th>Disease / Clinical features, diagnosis, and treatment</th>
<th>Q-Fever</th>
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<tbody>
<tr>
<td><strong>Features:</strong> 1. Caused by Coxiella burnetii (Gram⁺) transmitted by inhalation of infected material (aerosol), blood, ingestion of infected milk; found in the placenta of cattle, sheep, and goats. 2. Acute: low fever, headache, myalgias, atypical pneumonia. (3) Chronic (complications): chronic hepatitis or endocarditis. <strong>Dx:</strong> Most cases are self-limited within 2 weeks. Confirmation diagnosis can be made by specific serologic antibody tests if necessary. <strong>Tx:</strong> Acute, symptomatic cases — doxycycline. Chronic/complications: hydroxychloroquine plus doxycycline (&gt; 18 mo for endocarditis).</td>
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<th>Brucellosis</th>
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<tr>
<td><strong>Features:</strong> 1. Also called Undulant Fever, caused by Brucella Spp. (a Gram⁺ bacillus) from dairy products or contact with animals. 2. Prolonged fever, sweating, joint pain, enlarged LN, and hepatosplenomegaly. <strong>Dx:</strong> Pathologic culture and serologic tests (+). <strong>Tx:</strong> Doxycycline plus rifampin.</td>
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<th>Tularemia</th>
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<td><strong>Features:</strong> 1. Caused by Francisella tularensis (a Gram- bacillus) by tick bite, mediated by rabbits, deers, etc. 2. There are different types: ulceration, pneumonia, and typhoid; presenting with fever, painful focal ulceration, papules, or enlarged LN with tenderness. <strong>Dx:</strong> Serologic antibody (+). <strong>Tx:</strong> Streptomycin/gentamicin/doxycycline.</td>
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<th>Cellulitis and Erysipelas</th>
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<tr>
<td><strong>Features:</strong> 1. Mostly caused by beta-hemolytic Streptococcus (A, B, C, G, and F), Staph-A (#1) or Pasteurella multocida through an animal bite (“Cat-dog-man biting disease”). 2. Red, hot, swollen and tender skin lesion; with a clear border—erysipelas; without clear border—cellulitis. <strong>Dx:</strong> Clinical manifestations. Cultures are necessary only for extensive or special lesions. <strong>Tx:</strong> Dicloxacillin, augmentin (amoxicillin + clavulanate), clindamycin, or cefazolin.</td>
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<th>“Cat-scratch disease”</th>
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<tr>
<td><strong>Features:</strong> 1. Caused by Bartonella Hens. (a Gram⁺ bacillus) 2. Fever, painful focal lesion and enlarged cervical LN with or without tenderness. <strong>Dx:</strong> Clinical manifestations. <strong>Tx:</strong> Mostly self-limited. For severe cases, treat with azithromycin or doxycycline.</td>
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<th>Plague</th>
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<td><strong>Features:</strong> 1. A highly contagious disease caused by Yersinia pestis (a Gram⁺ bacillus) through flea bite from rodents (rats, mice, dogs), or respiratory tract. It can be co-infected between humans and animals. 2. Subtypes: (1) By skin wound, it causes bubonic (adenopathic) plague (&gt;80% of cases), with fever, chills, weakness, and headache, followed by intense pain and swelling in a lymph node. (2) By respiratory tract, it causes pneumonic plague. (3) Septicemic plague: may be without a preceding bubo, with high fever, shock, and death if not treated in time. <strong>Dx:</strong> Pathogen isolated or F1 Ab/Ag (+). <strong>Tx:</strong> Immediate supportive care and antibiotics (streptomycin, gentamicin, or doxycycline).</td>
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| Leptospirosis |
**Features:** 1. Caused by *Leptospira* spp. (spirochetes) through contaminated water by rodents and farm animals. 2. **Anicteric:** rash, lymphadenopathy, elevated LFTs; **icteric:** renal or/and hepatic failure, vasculitis. **Dx:** Mainly based on epidemiologic exposure and clinical manifestations; serology or culture may confirm if necessary. **Tx:** Oral **doxycycline**, **azithromycin**, or amoxicillin. Most cases are mild to moderate, with good prognosis.

**Ehrlichiosis**

**Features:** 1. Caused by *Ehrlichia* spp. (Gram-) through tick bite from deers, etc. 2. Fever, chills, malaise + rash; a few cases may be complicated with GI bleeding, renal injury, or ehrlichial meningitis. **Dx:** Clinical experience. **Tx:** Oral **doxycycline or tetracycline** for a week.
Chapter 1: High-yield Questions (HYQ)

1. A 10 y/o girl presents with fever, intermittent abdominal (Abd) pain and bloody diarrhea for the past 10 days after a local camping trip. She feels weak and fatigued. Stool analysis reveals WBC and RBC but no bacteria, ova or parasites, and two cultures on enteric pathogens are (-). P/E finds T = 38.5°C and a soft abdomen with mild RLQ tenderness. CBC results are normal (Nl). What’s the most likely diagnosis (Dx)?
   A. Traveler’s diarrhea    B. Cryptosporidiosis    C. Giardiasis
   D. Crohn disease          E. Dysentery

2. A 55 y/o woman presents with malaise, fever, and nausea for the past 2 days. She has been on chemotherapy for breast cancer for the past 3 months. She denies headache, chill, cough, and bone pain. P/E finds T = 38.7°C, HR = 90/min; other results are unremarkable. CBC reveals pancytopenia with WBC = 1,200/uL. Her CXR and urine analysis are normal. Blood and urine samples are taken for pathogen cultures. The best next step of treatment (Tx) is
   A. IV ceftazidime and vancomycin in hospital    B. IV cefepime and vancomycin in hospital
   C. IV cefepime in hospital                     D. IV gentamycin and vancomycin in hospital
   E. outpatient Tx with piperacillin             F. IV amphotericin B in hospital

3. A 65 y/o man presents with an abrupt fever, headache, dry cough, diarrhea, and abdominal pain for the past 10 hours. He lives alone in an old apartment with unsanitary conditions. P/E results are normal except for T = 38.5°C. CXR reveals bilateral infiltrates. WBC = 9,000/uL with left shift (increased ratio of immature neutrophils). There are no other abnormal findings. What’s the most likely cause?
   A. H. Inf (Hib)    B. Mycoplasma    C. Legionella
   D. Chlamydia      E. TB bacilli

4. A 27 y/o woman comes to the clinic one week after a trip to the Northeast (U.S.), and presents with mild fever, headache, and an expanding rash on the right foot. P/E finds T = 38°C, stable vital signs, and a 3-cm circular, erythematos, nontender rash with central clearing on the right foot. EKG reveals I’ A-V block. There are no other abnormal findings except for a 3-month pregnancy. What’s the most likely diagnosis?
   A. Cellulitis    B. Rocky Mountain spotted fever (RMSF)
   C. Lyme disease D. Tularemia      E. “Cat-scratch disease”

5. For the above patient (in Q4) who wishes to stay home after an immediate therapy, the most appropriate antibiotic treatment is
   A. oral azithromycin    B. oral doxycycline    C. oral amoxicillin
   D. IV PG                E. IV ceftriaxone

6. A 60 y/o woman is brought to the ER with fever, RUQ abdominal pain, and nausea and vomiting for the past 5 hours. P/E results: T = 39.5°C, HR = 90/min, marked RUQ abdominal tenderness on palpation and rebound tenderness. CBC reveals WBC = 18 x 10^3/uL with predominant neutrophils and bands. Ultrasound shows gallstones with dilated bile ducts and fluid. Her vital signs are stable. What’s the best initial treatment?
   A. Oral quinolones    B. IV quinolones    C. IV ceftazidime
   D. IV ampicillin      E. Support and observation in hospital
7. Continued with Q6: The patient still has persistent symptoms after 5 hours of the appropriate antibiotic treatment. What’s the best next step now?
A. Fluid and blood cultures  B. IV quinolones  C. IV cefepime  
D. IV ampicillin  E. ERCP

8. Continued with Q6-7: For the above patient, the proper tests show mixed Gram’ bacteria and anaerobes. At this time, the most appropriate antibiotic to be included is
A. clindamycin  B. quinolones  C. gentamycin  
D. ampicillin  E. metronidazole

9-10: A 68 y/o man is brought to the ER for high fever, headache, nausea, vomiting, and confusion. He had a small dental surgery 3 days ago. P/E results: Unclear consciousness, T = 39.5°C, HR = 90/min, RR = 25/min, BP is normal; neck is stiff; Kernig’s sign is suspicious. Sensation seems normal. Eye exam shows equal-sized, mildly dilated pupils and papilledema (by fundoscopy). Blood is taken for culture and sensitivity test. What’s the most appropriate next step?
A. A head MRI scan  B. LP for CSF assay and C/S  C. A head CT scan  
D. An empiric antibiotic  E. IV steroid

10. For the above patient, the most appropriate management has been done. Now the best medical treatment is intravenous administration of
A. large-dose PG  B. ceftazidime + vancomycin  C. ceftriaxone + vancomycin  
D. cefotaxime + ampicillin  E. ceftriaxone + ampicillin + vancomycin

11. A 70 y/o man is brought to the ER for fever, headache, and confusion for the past 2 days. He lives alone with poor living conditions. P/E results: Alert, T = 38°C, HR = 88/min, RR and BP are normal; neck is stiff; Kernig’s sign is suspicious. Eye exam is normal. CBC: WBC = 15 x 10^3/uL, with 50% LC. CSF: Opening pressure = 200 mmH2O, LC = 60%, neutrophils = 40%, protein = 55 mg/dL, and glucose = 30 mg/dL. This patient most likely has
A. pneumococcal meningitis  B. viral meningitis  C. TB meningitis  
D. TB encephalitis  E. fungal meningitis

12. A 16 y/o girl is brought to the ER for eye pain and blurred vision for the past 12 hours. She uses contact lens daily and follows the sanitary procedures most of the time. Eye exam shows a hazy cornea with central ulceration and adjacent stromal abscesses. Eye movement is normal. What’s the most likely diagnosis?
A. Bacterial keratitis  B. Fungal keratitis  C. CMV retinitis  
D. HSV retinitis  E. Orbital cellulitis

13. A 40 y/o man complains of (c/o) intermittent abdominal discomfort, decreased appetite, and 5 kg Wt loss for the past 3 months. He has a history of smoking and alcohol drinking for 5 years, and two previous blood transfusions. P/E results are mostly normal. Ultrasound (U/S) shows a normal liver image without any mass. Serology results: LFTs are normal; HBsAg, HBeAg, and anti-HBs, anti-HBc, and anti-HBe IgGs are all (+). What’s the best explanation?
A. Liver cell carcinoma  B. Chronic Hepatitis B, with low viral replication  
C. Chronic Hepatitis B, with active viral replication  D. Recovery from Hepatitis B, with immunity  
E. Chronic hepatitis B, with heterotypic Anti-HBs
14. A 25 y/o man suffered from a puncture wound of the right foot 3 days ago and now presents with fever and increased foot pain. P/E shows a swollen wound on the right ankle with tenderness on palpation. T = 39 °C, HR = 90/min, RR = 26/min; BP is normal. CBC shows WBC = 15 x 10^3/uL, with predominant neutrophils and bands. ESR = 120. Tech^99 is scheduled and blood samples are taken for culture and sensitivity test. What’s the best initial treatment?
A. Oxacillin
B. Vancomycin
C. Ceftriaxone
D. Cefotetan
E. Cefepime

15-16: 15. A 20 y/o sexually active man complains of 2-day’s sore throat, fever, swollen neck masses, and abdominal pain. He developed a generalized skin rash after taking ampicillin. He reports having used allopurinol for gout before the onset of these symptoms. P/E shows enlarged tonsils, cervical LNs, and spleen, and a maculopapular rash all over the body. T = 39°C. Vital signs are normal. More tests are scheduled. What’s the best explanation for his conditions?
A. Ampicillin allergy
B. Acute upper respiratory infection
C. Allopurinol allergy
D. Infectious mononucleosis
E. AIDS
F. Chlamydia infection

16. CBC for the above patient reports: hematocrits (HCT) = 44%, WBC = 8500/uL with many atypical cells, platelets = 85 x 10^3/uL. Monospot test is (+). Apart from bed rest, what’s the most appropriate next treatment?
A. Acyclovir
B. Ganciclovir
C. Steroids
D. PCN-G
E. Early exercise

17. A 20 y/o sexually active female presents with lower abdominal pain, dysuria, and increased, purulent vaginal secretions without odor. She has no fever or other symptoms. Pelvic exam shows a red cervix with mucus, and cervical motion tenderness. Urinalysis (U/A) shows WBC and protein. What’s the best next step?
A. Secretion test for chlamydia
B. Thayer-Martin for gonococcus
C. VDRL test for syphilis
D. KOH test for candida
E. Smear for Trichomonas

18. Continued from Q15: Fluorescent antibody test for chlamydia in Q15 has come out with (-), and Thayer-Martin for gonococcus is (+). Given this, the best treatment now is:
A. a single dose of ceftriaxone and azithromycin
B. a single dose of ceftriaxone
C. a single dose of ceftriaxone and doxycycline
D. cefoxitin IV + azithromycin PO
E. Ampicillin + gentamycin + metronidazole + clindamycin for 5 days

19. A 17 y/o girl presents with 3-day’s fever, headache, dry cough, and weakness. P/E is normal except for T = 38.5°C. Her urine dipstick testing reveals protein (+++) but no bacteria, RBC or WBC. What’s the best next step?
A. Serum BUN level
B. 24-hour collection of urinary protein
C. Urine culture for pathogens
D. Reassurance: “It’s common and benign.”
E. Repeating the dipstick test
20. A 60 y/o man presents with increased urinary frequency and urgency, and a sensation of suprapubic fullness but difficulties in voiding for the past 3 days. P/E finds an enlarged urinary bladder and an indurated, enlarged prostate with tenderness. Urinalysis is normal. Analysis for prostatic secretions reveals 18 WBCs/HPF (normal reference is <10), but cultures for bacteria are (-). Other results are unremarkable. A urinary catheter is inserted and 300 mL of urine is removed. What’s the most appropriate next step?

A. Repeating the secretion culture  B. Empirical TMP-SMX for E coli
C. Alpha-R blocker  D. Prostate specific antigen (PSA) testing
E. FNA of the Prostate

21. A 58 y/o man presents with fever, chills, right flank pain, and dysuria for the past 5 hours. He occasionally smokes and drinks alcohol. P/E finds T = 38.5°C, HR = 110/min, and percussion tenderness over the right renal area. CBC shows WBC = 15 x 10^3/uL with left shift. Urinalysis reveals WBC and protein. Urine is sent for culture and sensitivity test. He went home with prescribed oral ciprofloxacin. He comes back 3 days later with T = 38.3°C. What’s the most appropriate next step?

A. Increase the dose of oral ciprofloxacin  B. IV ciprofloxacin
C. IV cefepime  D. IV ampicillin + gentamycin
E. Renal CT scan

22. In the same month, a 30 y/o man experiences his 2nd onset of fever, chills, cough with sputum, and chest pain. He has a history of risky sexual behavior with both males and females for “several years.” P/E shows T = 39°C, HR = 110/min, and diffuse rales in the lungs. CXR reveals multiple lobar infiltrates. CBC shows WBC = 1200/uL and CD4 = 200/uL. Blood and sputum are taken for examination of pathogens. What’s the best initial treatment?

A. Azithromycin or erythromycin  B. Levofloxacin + erythromycin
C. Cefotaxime + imipenem  D. TMP-SMX
E. Ceftazidime + TMP-SMX

23-26: Match the following clinical scenarios with the most likely diagnosis.

A. Bacterial meningitis  B. Subacute sclerosing panencephalitis
C. Viral meningitis  D. AIDS encephalopathy
E. PML  F. Herpes encephalitis
G. CNS abscess  H. Malaria
I. Fulminant viral encephalitis  J. Fulminant hepatitis

23. A 25 y/o man is hospitalized for decreased memory and changes in mood for the past 3 weeks, with occasional right arm clonus. He had a history of fever and headache one month ago, but no trauma. P/E results: T = 39°C, alert. Neurologic exams: decreased recent memory, speech difficulties, and right hemiparesis. Lab tests: increased WBC and LC ratio. CSF: Opening pressure = 220 mmH2O, LC = 60%, neutrophils = 40%; culture is (-). EEG: Spike-and-wave discharges originating from the temporal lobe.

24. A 25 y/o man is hospitalized for a chronic bleeding disease and progressive memory loss. Severely low platelet counts have forced him to receive four times of urgent blood transfusions in a poorly equipped hospital over the past 5 years. Neurologic exams reveal poor recent and remote memory, decreased vision, gait ataxia, limb hyper-reflexia, and changes in mood and personality. T = 38.5°C. Head MRI is unremarkable.

25. A 25 y/o man is hospitalized for 1-month history of headache, fever, right arm clonus, memory loss, and changes in mood. He has been HIV (+) for the past 5 months. Neurological exams show decreased recent memory,
speech difficulties, and right hemiparesis. T=39°C, CSF-P = 220 mmH2O; culture is (-). CT with contrast reveals a mass in the left temporal lobe.

26. A 45 y/o man is back from a trip to the countryside with malaise, headache, confusion, periodic high fever, chills, and sweating for the past 3 days. P/E reveals T = 41°C, confused status, neck and limb stiffness, generalized rash and LN swellings, and hepatosplenomegaly. CBC reveals anemia, leukopenia, and reticulocytosis. Blood samples are taken for special tests.

27. Diagnosis of pathogen for the above patient in Question 23 is confirmed by immunoassay of the CSF. IV acyclovir was administered for the past 3 days and re-examination of the patient shows no changes in his conditions. What’s the most appropriate next step now?

A. Increase the dose of acyclovir  
B. Change to ceftriaxone  
C. Change to foscarnet  
D. Change to famciclovir  
E. Change to amphotericin B

28. A 65 y/o man has been undergoing 2-week’s chemotherapy for lymphoma. P/E finds T = 39°C and other results are (-). CBC shows WBC = 500/uL without bands. The most appropriate next step is to

A. wait for the results of blood culture and sensitivity test to give the correct antibiotics  
B. give oral agents to prevent bacterial and fungal infections  
C. give IV agents to prevent bacterial and fungal infections  
D. give broad-spectrum antibiotics to cover Gram- bacteria, Pseudomonas, and Staph-aureus  
E. take blood samples for culture and sensitivity test

29. A 25 y/o female working in a day care center develops a pruritic rash in crops over her whole body except the palms and soles, with fever, headache, cough, and dyspnea for the past 3 days. She claims that she has received all of the appropriate pediatric immunizations. P/E finds T = 39°C, generalized small vesicles on erythematous bases with crusting, and rales heard over the lungs. CBC is awaited. This patient most likely

A. has about normal CXR result  
B. will infect her husband soon  
C. has leukocytosis  
D. will have life-time immunity after recovery  
E. has missed a vaccine in the childhood

30. A 15 y/o girl has just returned from a spring camping trip and presents with irritating red eyes and copious watery discharge from the eyes and nose. P/E reveals a mild fever, tachycardia, and congested conjunctiva and nasal membranes. There are no other abnormal findings. The most likely cause is

A. allergy  
B. bacterium  
C. chlamydia  
D. virus  
E. foreign body

31. A 16 y/o boy has just returned from a spring camping trip and presents with painful red eyes with copious watery discharge. P/E reveals a mild fever, tachycardia, and congested conjunctiva. Funduscoppy shows retinal pallor and ulceration. There are no other abnormal findings. The most likely etiology is

A. CMV  
B. HSV  
C. chlamydia  
D. candida  
E. allergy
32. A 25 y/o man presents with headache and a painful swelling localized to the left eyelid with tenderness, which is not associated with eye movement. There is no conjunctival congestion or discharge, nor other abnormal findings. He claims he has “two girl-friends.” The most likely diagnosis is

A. orbital cellulitis  
B. post-orbital cellulitis  
C. dacyrocystitis  
D. hordeolum  
E. chalazion

33. A 45 y/o man presents with fever, abdominal pain, nausea, and loose stools of yellowish color for the past 3 days, beginning after he eat a large meal with friends. None of his friends has similar symptoms. He has a 5-year history of smoking, alcohol consumption, and decreased Wt. P/E finds a moderate fever and a firm, distended abdomen with decreased bowel sounds, tenderness on deep palpation, and with rebound tenderness. Ascites is (+) and the spleen is enlarged. What’s the most important next test to determine the etiology?

A. Abdominal ultrasound  
B. CBC  
C. Ascites analysis  
D. Abdominal CT scan  
E. Stool analysis

34. A 25 y/o female presents with fatigue, decreased appetite, nausea, and yellow urine for the past week. Her LMP was 4 weeks ago. P/E finds normal vital signs, jaundice, flat and soft abdomen, and an enlarged liver. Serum ALT and bilirubin are elevated; beta-hCG is (-); anti-HAV IgM and HBsAg are (-); anti-HAV IgG, anti-HBc IgM, and HBeAg are all (+). What’s the most likely Dx?

A. Acute hepatitis A with HBV carrier  
B. Acute hepatitis B with HAV immunity  
C. Acute hepatitis A and B  
D. Acute hepatitis B with HAV carrier  
E. HBV carrier with HAV immunity

35. A 40 y/o man presents with low-grade fever, sweats, coughs with blood-tinged sputum, right chest pain, and decreased Wt for the past month. He has a history of smoking and alcohol use for the past 5 years. P/E finds T = 38°C, normal vital signs, decreased respiratory sounds, and dullness on percussion of the right lower chest. CBC reveals anemia and increased WBC and LC%. CXR shows diffuse infiltrates in the right lower lung. The most appropriate next test for Dx is

A. Serology tests  
B. chest CT  
C. sputum culture  
D. PPD test  
E. sputum stain for acid fast bacilli

36-41: Match the following clinical scenarios with the most likely etiology.

A. Klebsiella granulomatis  
B. H. ducreyi  
C. Chlamydia  
D. HSV  
E. HPV  
F. Poxvirus  
G. Candida  
H. T. pallidum  
I. Gonococcus  
J. Allergy

36. A sexually active female presents with multiple soft, fast growing, pedunculated, and pink papules of 3-4 mm in size on the vulva for the past week. There are no other abnormal findings.

37. A sexually active female presents with multiple red, painful, and itchy vesicles with circular, scarring ulcers on the vulva for the past 2 weeks. Tissue is taken for Tzanck test and culture.

38. A sexually active female presents with a week of multiple painless, shallow, circular ulcers on the vulva, with low-grade fever, dysuria, tender swelling of the left inguinal lymph nodes, and a purulent draining sinus. A sample from the ulcer is taken for smear stain and fluorescent tests.
39. A sexually active female presents with a week of multiple painful, irregular, deep papules and ulcers on the vulva with a bad odor, and left inguinal LN suppuration. There are no other abnormal findings. A sample from the ulcer is taken for a Gram stain.

40. A sexually active female presents with a week of multiple raised, red, painless papules (0.5-1cm) with granulomatous ulcers on the vulva. There are no other abnormal findings. A sample from the ulcer is taken for a pathologic stain.

41. A sexually active man presents with low-grade fever, diffuse and symmetric pink papules, and painless lymph node swellings in both inguinal areas. The patient reports finding a small painless smooth ulcer on his penis one month ago, which has now disappeared. Specific serology confirms the Dx.

42. A 17 y/o girl is brought to the ER with fever, nausea, vomiting, dizziness, abdominal pain, knee pain, and weakness. She was travelling in another city 5 days ago with her boyfriend and reveals that her LMP occurred during the trip. P/E results: Alert, T = 39°C, HR = 95/min, BP = 90/55 mmHg; soft neck, desquamative rash on hands and feet, and tenderness on the middle abdomen and both knees without swellings. IV fluid is started, and urine and blood samples are taken for culture and sensitivity test. The most appropriate next step is

A. IV nafcillin  
B. IV ceftriaxone  
C. blood culture and sensitivity test  
D. joint fluid aspiration  
E. abdominal U/S

43. A 30 y/o female with multiple pets presents with fever, dry cough, chest pain, and shortness of breath for the past 3 days. P/E results: Alert, T = 39°C, RR = 28/min, HR = 90/min; BP is normal; rough respiratory sounds. WBC is 12,000/uL. CXR reveals interstitial infiltrates. What’s the best initial treatment?

A. Erythromycin  
B. Doxycycline  
C. Levofloxacin  
D. Azithromycin  
E. Amoxicillin

44. A 60 y/o female presents with fever, headache, dry cough, and loss of appetite that began after attending a party 3 days ago. Two other friends from the party also have similar symptoms. P/E shows T = 38.5°C and there are no other abnormal findings. What’s the most appropriate next step?

A. Amantadine for 4-5 days  
B. Oseltamivir for 4-5 days  
C. Amoxicillin for 4-5 days  
D. Annual flu vaccination  
E. Blood culture and sensitivity test

45-50: Match the following clinical scenarios with the most likely cause.

A. Campylobacter jejuni  
B. E. coli (O157:H7)  
C. Staph-aureus  
D. Shigella  
E. Salmonella  
F. Enterotoxigenic E. coli  
G. Giardia  
H. Bacillus cereus  
I. Clostridium perfringens  
J. Clostridium difficile  
K. Clostridium botulinum  
L. Vibrio parahaemolyticus  
M. Yersinia enterocolitica  
N. Proteus  
O. Klebsiella

45. A 17 y/o boy has ingested a cup of leftover milk at home. Four hrs later, he has severe lower abdominal cramps and loose stools with sparse blood and mucus. There is no vomiting. P/E finds T = 38°C and a soft abdomen with mild RLQ tenderness. Stool analysis reveals WBC and RBC. CBC results are normal.
46. A 10 y/o boy has had a meal of reheated rice in a friend’s home. Two hrs later, he has severe nausea, vomiting, and upper abdominal cramps. He has one relatively loose stool during the day. P/E finds no fever or other abnormal results. Stool analysis and CBC results are normal.

47. A 16 y/o boy joined a lunch with all types of foods (including seafood) in an unsanitary restaurant. In the evening he presents with severe, recurrent lower abdominal cramps and loose stools with blood and mucus for a few hrs. He has nausea and sensation of urgently passing stools. There is no vomiting. P/E finds T = 39°C and the lower abdomen is soft with tenderness. Stool analysis shows WBC and RBC. CBC reveals leukocytosis.

48. A 15 y/o boy has had a lunch in an unsanitary restaurant. In the evening, he has abrupt profuse, watery diarrhea. There is no vomiting, abdominal cramp, or fever. He’s been using amoxicillin for otitis media for the past 10 days. P/E results are unremarkable. Stool toxin test is (+). CBC is normal.

49. A 17 y/o girl has joined a lunch in a Japanese restaurant and had fresh raw fish. In the evening, she has fever, nausea, severe lower abdominal cramps, and diarrhea with blood and mucus. P/E finds T = 38.5°C and a soft abdomen with RLQ tenderness. Stool analysis reveals WBC and RBC. CBC reveals leukocytosis.

50. A 20 y/o newly married female presents with urinary frequency, urgency, and burning sensation for a day. She denies any fever, flank pain, or abnormal vaginal discharge. She also denies any history of UTI or STD. P/E results are about normal. Urine analysis reveals WBC and alkalosis. CBC is normal.

51. A 22 y/o married female comes to the clinic for a general health exam, and found herself about 5-week pregnant confirmed by a (+) blood HCG test. She took rubella immunization 6 weeks ago and has been using contraception to her best efforts because the physician has advised her to avoid pregnancy within 3 months. She is generally healthy and concerned about the options of avoiding harm to the fetus. What’s your best next step of management?
   A. Advise abortion
   B. Reassurance
   C. IV immunoglobulin
   D. Pelvic ultrasound
   E. Explain the risks and benefits of abortion and let the patient decide

52. A 30 y/o sexually active man presents with fever, fatigue, and skin rash for the past few days. He was HIV (+) two years ago but has had no obvious symptoms until now. P/E shows T = 38.5°C, normal vital sign, and multiple non-tender, 1-1.5 cm, round, reddish, vascular papules on both arms. What’s the most likely diagnosis?
   A. Molluscum contagiosum (MC)
   B. Common warts
   C. Herpes simplex
   D. Kaposi sarcoma (KS)
   E. Bacillary angiomatosis

53. A 25 y/o woman presents with painful, swollen left knee for the past 3 days. She cannot think of any significant events related to it. She denies any abnormal urinary or vaginal discharges, or history of trauma, diseases or drug use. Careful history taking reveals that she has several sexual partners and she uses condoms most of the times. P/E finds low fever, tachycardia, and a swollen left knee with tenderness and limited range of motion. Arthrocentesis: WBC = 85 x 10^3/uL with 88% neutrophils. Gram staining of the joint aspirate is (-). Urinalysis is normal. What’s the best next step for diagnosis?
   A. Blood culture
   B. Urine culture
   C. Culture of the joint aspirate
   D. Culture of the vaginal discharge
   E. Culture of urethral swab

54. A 60 y/o man has been hospitalized for the treatment of diabetes for the past 2 weeks. He has a history of smoking and alcohol drinking for 10 years. Today he presents with fever, cough with yellowish sputum, chest pain, tachypnea, and dyspnea. P/E results: T = 38.8°C, RR = 28/min, HR = 90/min; BP is normal; respiratory rales are (+)
in both lungs. CBC reveals HCT = 40%, WBC = 12 x 10^3/uL, neutrophils = 88%. CXR shows multiple infiltrates in both lungs. Sputum is taken for Gram stain and culture. Which of the following is NOT a common pathogen for this patient?

A. Pneumococcus  
B. Staph-aureus  
C. E. coli  
D. Pseudomonas  
E. Hib  
F. Klebsiella

55. A 30 y/o man presents with malaise, general muscle pain, and decreased appetite for the past month. He has a 5-year history of smoking, alcohol drinking, and IV drug abuse. P/E results are unremarkable. CBC reveals HCT = 38%, WBC = 6,000/uL, LC = 44%, platelets = 100 x 10^3/uL. Anti-HCV is (+) and LFTs are normal. Test of HCV RNA load by PCR is started. Which of the following is NOT commonly associated with the patient’s disease?

A. Mixed cryoglobulinemia  
B. Polyarteritis nodosa  
C. Sjogren syndrome  
D. Hashimoto thyroiditis  
E. Membrane glomerulonephritis  
F. ITP  
G. Plasmacytoma  
H. T-C lymphoma

56. In a pre-term exam, an asymptomatic pregnant patient has been found that the HBsAg, anti-HBe and anti-HBc IgGs are (+), and HBeAg and anti-HBs IgG are (-). There are no other abnormal findings. For this patient’s conditions, all the following should be administered immediately after delivery EXCEPT

A. IV HBIG to the newborn  
B. HBV vaccine to the newborn  
C. HBV vaccine to the mother  
D. Ribavirin to the mother  
E. Alpha-interferon to the mother

57. A 55 y/o man with immunodeficiency presents with malaise, fever, night sweats, and cough with yellow sputum over the past week. He has been on antibiotic prophylaxis for the past 2 months. P/E results: Alert, T = 39°C, RR = 28/min, HR = 90/min; BP is normal; respiratory sounds are rough. CBC reveals HCT = 32%, WBC = 8,000/uL, neutrophils = 85%, LC = 9%. Skin PPD is 9 mm induration. CXR shows left lobe cavitation. Sputum smear reveals weakly acid-fast filamentous branching rods. What’s the most likely cause of the disease?

A. Actinomyces  
B. Nocardia  
C. TB  
D. Coccidioides  
E. Blastomyces  
F. Histoplasma

58. A 10 y/o boy is brought to the clinic an hr after he was bitten by a neighbor’s dog due to his provocation. The dog did not get rabies immunization and is not showing any abnormal symptoms. P/E finds a tender swollen lesion without bleeding on the left forearm of the boy. His wound is cleaned with iodine. The most appropriate next step is

A. observe the dog for 10 days  
B. kill the dog and perform the brain biopsy  
C. give the boy IV immunoglobulin  
D. give the boy active rabies immunization  
E. give the boy active and passive immunization  
F. give reassurance

59. During a fight at school, a 9 y/o boy received a bite on the right forearm by another boy, and is brought to the clinic an hour later. His records show up-to-date immunizations. P/E finds a swollen tender lesion with tiny bleeding on the right forearm. There are no other abnormal findings. Apart from cleaning the wound, the best next treatment is

A. observation  
B. amoxicillin  
C. ampicillin + clavulanate  
D. amoxicillin + clavulanate  
E. clindamycin  
F. erythromycin

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60. In medical records, human bites have been shown to transmit all the following infections EXCEPT

A. hepatitis B
B. hepatitis C
C. herpes simplex
D. syphilis
E. TB
F. actinomycosis
G. tetanus
H. AIDS

Answers and Explanations for Chapter 1 HYQ

1. (D). Regional enteritis (Crohn disease), ulcerative colitis, dysentery and invasive E. coli (O157:H7) can all cause bloody diarrhea and fever. Two negative stool cultures in this case may exclude infection. Traveler’s diarrhea, cryptosporidiosis and giardiasis usually cause small bowel infection with watery diarrhea.

2. (C). This is an urgent case of febrile neutropenia induced by chemotherapy that requires immediate antibiotic treatment in hospital. Empiric treatment usually includes monotherapy of ceftazidime, cefepime, or a carbapenem, or combination therapy of piperacillin plus gentamycin, to cover Gram’ bacteria (especially Pseudomonas). Vancomycin is usually added for resistant Staph-aureus or Strep-P or severe skin/mucosa infections. If fever persists despite above treatment, amphotericin B is added to cover suspected systemic fungal infection. ‘E’ is inadequate.

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Chapter 16

MENTAL AND BEHAVIORAL DISORDERS

(Mainly by DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Ed, 2014)

BASICS

Psychiatry is the medical specialty devoted to the study and treatment of mental disorders, which include various affective, behavioral, cognitive, and perceptual disorders.

Mental Status Examination (MSE)

MSE is used to describe the physician’s observation and impression of the patient during the interview. Combined with the patient’s history (Hx), it is the best way to make an accurate diagnosis (Dx) for most psychiatric diseases and disorders.

MSE includes appearance, attitude, behavior, mood (emotions perceived), affect (emotional responses), thought (form and content), speech, sensorium (alertness, level of consciousness, and orientation), cognition (memory, concentration, capacity to read, write and learn, abstract thinking, judgment, and insight), reliability, and self-control ability.

Neuropsychological tests used to detect organicity from any psychiatric disorder include Bender-Gestalt, Luria-Nebraska, and Halted-Reitan tests.

Interviewing Techniques

Open-Ended Questions: Allow patient to speak in his own words as much as possible. E.g., “Can you tell me more about this?”

Closed-Ended Questions: Ask for specific information without much choice in answering. E.g., “Are you feeling the pain now?”

Facilitation: The physician helps the patient continue by providing verbal or nonverbal clues. E.g., “Yes, continue, please.”

Confrontation: The doctor points something out to the patient directly. E.g., “You look angry today. I’d like to know why.”

Reassurance: If it’s truthful it can lead to increased compliance, but if it’s false it can lead to decreased compliance. E.g., “His conditions are serious, but we’ll do our best to treat it.” (True) “Don’t worry. Everything will be fine.” (False)

Leading: The answer is suggested in the question. E.g., “Is the voice telling you to kill yourself?”
**Defense Mechanisms**

The way and means that the ego reduces anxiety and controls instinctive urges and unpleasant affects (emotions). Most defense mechanisms are unconscious (except suppression), discrete, and dynamic, and can be adaptive or maladaptive.

**Types of Defense Mechanisms**

**Acting out:** The outburst display of previously inhibited emotions or behavior (often in actions rather than words); usually considered to be healthy and therapeutic. E.g., harshly criticized by his father, the boy had a temper tantrum.

**Blocking:** Temporary block in thinking. E.g., “What were we talking about?”

**Denial:** A defense used to avoid becoming aware of some painful aspect of reality. E.g., “I know they gave me a wrong diagnosis as cancer.”

**Displacement:** An emotion or drive is shifted to another object with similar but with more tolerable nature. E.g., someone kicked the dog after having a fight with his supervisor.

**Humor:** A mature defense: permitting the expression of feelings and thoughts with comfort or release to self and others. E.g., a patient said to the doctor, “It’s good that I have all these conditions to keep you busy.”

**Introjection:** Features of the external world are taken into part of the self. E.g., a secretary dresses like her supervisor.

**Intellectualization:** Excessive use of intellectual processes to avoid affective expression or experience. E.g., “It’s interesting to see there are more people getting the same cancer as mine.”

**Isolation:** Separation of an idea from the affect that accompanies it. E.g., when he saw the dead body of a friend, he appeared to show no emotion.

**Projection:** Attributing one’s own wishes, thoughts, or feelings onto someone else. E.g., (1) “I’m sure he did it intentionally!” (2) A nurse has been ignoring a patient with late-stage cancer, and replied when asked why, “He wants to be left alone.” (It is actually the nurse who wants to be alone. If she made excuses for ignoring the patient, it’s ‘rationalization”).

**Regression:** Returning to an earlier stage of immature behaviour. E.g., a 66 y/o physician begins to help his colleague occupy a seat at a routine meeting.

**Repression:** An idea or feeling is withheld from consciousness; unconscious forgetting. E.g., someone said he did not remember the car accident he had 2 years ago.

**Reaction formation:** An unacceptable impulse is transformed into its opposite, resulting in the formation of character traits. E.g., a frustrated man smiled at his supervisor after an immediate fight with a co-worker.

**Rationalization:** Using rational explanations to justify unacceptable attitudes, beliefs, or behaviors. E.g., “It’s good I lost the job so that I have more time to do exercise.”
**Somatization:** Psychic distress is converted into bodily symptoms. E.g., after hearing the bad news, she suddenly became blind.

**Splitting:** Dividing external objects into all good or all bad categories. E.g., “All car dealers are cheaters!”

**Sublimation:** Most mature defense. Instincts are led to change the aim or object from unacceptable to acceptable, to achieve impulse gratification. E.g., a boy who enjoyed ripping things becomes a surgeon.

**Suppression:** Conscious forgetting; the only conscious defense mechanism. E.g., “After becoming a Christian, Peter forgave his colleague’s insult and made a good friend with him.”

**Undoing:** It’s an “after behavior” -- trying to “undo” an unhealthy, destructive, or unacceptable thought or action by acting out or engaging in the contrary behavior that is more acceptable. E.g., (1) a man quit smoking and alcohol drinking and advocated his friends to do so; (2) a man insulted someone but immediately gave praising words.

**NEURODEVELOPMENTAL DISORDERS**

**Intellectual Disability**

**Definition:** Previously known as Mental retardation, also as Intellectual developmental disorder, it is defined as intelligence quotient (IQ) < 70, significantly decreased intellectual function (such as cognitive abilities), and must be accompanied by concurrent impairment in adapting to demands in school, work, social, and other environments. The onset is before 18 y/a, accounts for about 1% of the population, and is more common in school-age boys.

**Etiology**

Down syndrome, velocarionficial syndrome, and fetal alcohol syndrome are the three most common inborn causes. Other causes include genetic and chromosomal abnormalities (lipidoses, aminoacidurias, glycogen storage diseases, cri du chat syndrome, and fragile X syndrome); intrauterine or postnatal exposure to infections (rubella or CMV), toxins, alcohol, hypoxia, malnutrition (iodine deficiency, etc), heavy metals, physical trauma, and social deprivation.

**Essentials of diagnosis**

1. **Mild intellectual disability (IQ 50–69):** Patient attains academic skills to elementary 6th-grade level; can live independently or with minimal supervision; may have problems with impulse control and self-esteem; associated with conduct disorders, drug abuse, and ADHD.

2. **Moderate intellectual disability (IQ 35-49):** Academic skills to a 2nd-grade level; may be able to manage activities of daily living and working with serious supervision, and have significant problems conforming to social norms. Patient with Down syndrome has higher risk of early development of Alzheimer disease.
3. **Severe (IQ 20-34) and profound intellectual disability (IQ < 20):** Little or no speech, very limited abilities to manage self-care; requires more intensive support and a continuously, highly supervised environment.

4. **P/E** may show evidence of underlying disorder or injury. **Amniocentesis** may reveal chromosomal abnormalities associated with intellectual disability in high-risk pregnancies (mother >35 y/a).

**Differential diagnosis**

Borderline intellectual functioning (IQ 70-100), learning disorders, autistic disorder, sensory impairment, and environmental deprivation.

**Treatment**

1. Primary prevention such as genetic counselling, good prenatal care, and safe environments for expectant mothers.

2. Treating associated disease may improve level of cognitive and adaptive function. Special education techniques and behavioral therapy may improve ultimate level of function.

**Global Developmental Delay (GDD)**

**Definition:** GDD is a generalized intellectual disability that is usually characterized by lower than average intellectual functioning along with significant limitations in at least two other areas of development. Common signs include delayed acquisition of milestones (e.g., sitting up, crawling, walking), limited reasoning or conceptual abilities, poor social skills and judgement, aggressive behavior as a coping skill, and communication difficulties.

**Etiology and risk factors**

These include genetic (Fragile X syndrome), metabolic (PKU, etc), prenatal (rubella or birth trauma), perinatal (prematurity, injury, or infection). Sometimes the cause is unknown.

**Treatment**

Treat underlying cause.

**SPECIFIC LEARNING DISORDER AND LANGUAGE DISORDER**

**Definition:** Learning achievements in specific areas are substantially below expectations, considering the patient’s age, intelligence, sensory abilities, and educational experience. Types include reading disorder (No.1 common), math disorder, and written expression disorder.

**Etiology and risk factors**

There is more association with males, genetic factors, low socioeconomic status (SES), and coexisting conditions (cerebral palsy, lead poisoning and fetal alcohol syndrome). Many cases have no obvious causes found. Prevalence is 5% among school-age children.

**Essentials of diagnosis**
1. Onset is usually during elementary school, presenting with reading, math, or written expression disorder; poor self-esteem and social-maturity, school failure, and behavioral disturbances may occur. It may persist into adulthood.

2. Perceptual-motor problems, conduct disorder, oppositional defiant disorder (ODD), and ADHD may be present.

3. IQ and academic achievement tests are the major diagnostic tools.

**Differential diagnosis**

It’s necessary to rule out hearing or vision impairment, environmental deprivation, and mental retardation.

**Treatment**

The main treatment is special education (remedial or individual classes; quality instructions) to improve general learning and skills in the deficient areas. Counselling of patients and families to improve self-esteem, social behavior, and family functioning is helpful.

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**COMMUNICATION DISORDERS**

**Phonological disorder and stuttering** are now called communication disorders—which include language disorder, speech sound disorder, childhood-onset fluency disorder, and a new condition characterized by impaired social verbal and nonverbal communication called **social (pragmatic) communication disorder**. They should be treated by speech therapists according to individual’s needs.

**Attention-Deficit Hyperactivity Disorder**

It is a disorder characterized by inattention, short attention span, hyperactivity, and impulsivity that interfere with daily social or academic functioning in school and at home. Prevalence is 3-5% in school-age children; male:female = 9:1. The onset is mostly before 7 y/a, and symptoms persist throughout childhood (about 30% into adulthood).

**Etiology**

Unknown. It may be Assoc/w family history, trauma, and other disorders—mood and anxiety disorder, drug abuse, antisocial personality disorder, conduct disorder, and learning disorder.

**Essentials of diagnosis**

1. A child with ADHD usually presents with symptoms both in school and at home, and causes marked social and academic impairment for over 6 months.

2. Multiple symptoms of attention deficits: Short attention span for schoolwork, play or eating, difficulty following instructions or staying quiet, easily distracted and forgetting, and poor school performance and relationships with siblings.

3. Multiple symptoms of hyperactivity and impulsivity: Fidgety and over-active, unexpectedly leaving and running around, excessive talk, interrupting others, disobedient, and fighting.
4. IQ tests and structured symptom-rating scales: Useful for teachers and parents.

**Differential diagnosis**

Major rule-outs: Normal active behavior, adverse effects (S/E) of drugs, brain trauma, conduct disorder, autistic disorder, and mood disorders.

**Treatment**

1. Initial treatment should be non-medical -- psychobehavioral. Behavior therapy and environmental changes that can be used by parents or teachers to shape the behavior of children with ADHD include:
   - Maintaining a daily schedule; reducing distractions; setting small, reachable goals; providing places for the child to keep his personal things; rewarding positive behavior; using charts/checklists and calm discipline; limiting choices; encouraging healthy activities (sports, hobbies).
   - Medical treatment: Psychostimulants (methylphenidate, amphetamine, or pemoline) can effectively alleviate ADHD, given only on school days. S/E: Headache, tics, decreased appetite, sleep, and growth rate. If there is no response to psychostimulants or no tolerance to the adverse effects, an antidepressant, atomoxetine (a norepinephrine reuptake inhibitor) or desipramine (a TCA) may be effective.
   
2. Combined psychobehavioral and medical treatment is better than a single therapy.

**AUTISM SPECTRUM DISORDER (ASD)**

Previously it was in Pervasive Developmental Disorders (PDDs) and known as autism or autistic disorder. ASD is a neurodevelopmental disorder characterized by (1) persistent deficits in social communication and interaction and (2) restricted, repetitive patterns of behavior, interests, or activities in early childhood (mostly before age 3). ASD is four times more common in boys than in girls.

**Etiology**

Unclear; may be associated with genetics, environmental causes (heavy metals, pesticides, or childhood vaccines), CNS damage, and other diseases (encephalitis, maternal rubella, perinatal anoxia, phenylketonuria, tuberous sclerosis, fragile X syndrome). All these can affect brain development and information processing in the brain. No obvious causes are found in many cases.

**Essentials of diagnosis**

1. ASD-specific screening tests should be used in children with (1) delayed language/communication milestones; (2) regression in social or language skills; (3) a sibling diagnosed with ASD; (4) ages of 18-24 months; (5) concerns by parents or care providers regarding ASD.

2. **Diagnostic criteria** —requiring all of the following three aspects:
   - (1) Persistent deficits in social communication (verbal and non-verbal) and social interaction in multiple settings; demonstrated by deficits in all three of the following:
     - A. Social-emotional reciprocity (eg, absent or bizarre use of speech);
     - B. Nonverbal communicative behaviors used for social interaction (eg, abnormal eye contact or body language);
     - C. Developing,
maintaining, and understanding relationships (eg, difficulty adjusting behavior to social setting; difficulty making friends with peers).

(2) Restricted, repetitive patterns of behavior, interests, or activities; demonstrated by $\geq 2$ of the following:

A. Stereotyped or repetitive movements, use of objects, or speech; B. Insistence on sameness, unwavering adherence to routines, or ritualized patterns of behavior; C. Highly restricted, fixated interests that are abnormal in strength or focus (eg, bizarre manners, swinging and bumping, attracted by inanimate objects); D. Bizarre response to the environment (sounds, smells, temperature, etc).

(3) The symptoms must impair social or academic functions, exist in the early developmental period, and not better explained by intellectual disability or global developmental delay, although intellectual disability may be present in about 75% of cases.

3. P/E: May show evidence of self-injuries by head banging or biting, or by seizures.

4. Lab tests: May reveal abnormal EEG and brain morphology.

5. Course: About 30% of patients become semi-independent in adulthood, but almost all have severe residual disabilities. Poor outcome is associated with intellectual disability and speech failure.

**Differential diagnosis**

Major rule-outs: intellectual disability, hearing impairment, environmental deprivation, and selective mutism.

**Treatment**

It mainly includes family counseling, special education and behavior training. Antipsychotics can be used to control episodes of severe agitation or self-destructive behavior.

**Asperger Disorder (Syndrome)**

It is considered a milder form of autism spectrum disorder, more common in school age boys. Clinical features include extreme behavioral rigidity, perseverative/obsessive interests in a single object/topic and rules; with deficits in social interactions and behaviors, but not in language or intelligence.

**Treatment** is improvement of relationship with others.

**Rett Syndrome**

In DSM-4, it is a neurodevelopmental disorder of the grey matter of the brain that almost exclusively affects girls. Clinical features include a period of initially normal development followed by loss of normal speech and purposeful hand use, stereotypic hand movements, gait abnormalities (ataxia), and psychomotor disabilities. Additional features include deceleration of head growth, seizures, autistic features, and breathing abnormalities. Most cases result from mutations in the MECP2 gene.

**Treatment**

Symptomatic therapy; behavioral therapy for self-injurious behavior; physical therapy for muscular dysfunction.
MOTOR DISORDERS

A new sub-category, motor disorders, encompasses development coordination disorder, stereotypic movement disorder, and the tic disorders including Tourette disorder (syndrome).

Tourette Disorder

It is characterized by the onset of multiple motor and vocal tics in childhood (before the age 18), lasting more than one year. Prevalence is male:female = 3:1. The average onset age is 7. The course can fluctuate for many years.

Etiology

Mixed genetics may be associated, and may include abnormality in the dopaminergic (DA) and adrenergic system, ADHD and obsessive-compulsive disorder (OCD).

Essentials of diagnosis

1. Motor tics: Usually involve the muscles of the face and neck, presenting with head shaking, blinking, or twitching of the face, trunk, or extremities. It may also involve complex behaviors such as grimacing, swearing at people, pacing, touching, etc.
2. Vocal tics: Commonly include grunting, coprolalia, counting, throat clearing, etc.
3. Chronic multiple motor and vocal tics: Over 1 year and before 18 y/a, with remissions and exacerbations.

Treatment

A high-potency antipsychotic (risperidone, pimozide or haloperidol) is the No.1 therapy. Clonidine and clonazepam may also help.

ELIMINATION DISORDERS

Enuresis

It is a disorder characterized by repeated urine voiding into the patient’s clothes or bed usually at night in a child > 6 y/a. Diagnosis is by excluding a medical condition, and considering possible etiology of psychological stress, UTI or UT-defects, and Family history of enuresis. Prevalence is 3%.

Treatment

1. It’s important to reduce the patient’s emotional stress and reward the child for “a dry bed/clothes day,” to practice appropriate toilet training and to avoid large amounts of fluids before bed. A bell-pad may be used.
2. Medications: Desmopressin (DDAVP, No.1) or imipramine (No.2) is good for short-term effect.
Encopresis

Encopresis, also called stool holding/soiling, or paradoxical diarrhea, is voluntary or involuntary fecal soiling in children who have usually already been toilet trained. It usually occurs when a child after age 4 resists having bowel movements, as a symptom of chronic constipation.

**Diagnosis:** When encopresis occurs (1) in a child > 4 y/a at least once a month for > 3 months; (2) in inappropriate places (e.g., clothing or floor); (3) without a general medical condition, it may be diagnosed as a developmental or emotional disorder (elimination disorder).

**Treatment:** It can usually be treated successfully with patient positive reinforcement.

DISRUPTIVE, IMPULSE-CONTROL, AND CONDUCT DISORDERS

(ICD-10: Habit and Impulse Disorders)

This group of disorders involves problems in the self-control of emotions and behaviors, in which individuals are unable to resist an impulse. Different from other emotional and/or behavioral disorders, this group is unique in that these problems are manifested in behaviors that violate the rights of others (e.g., aggression, destruction) and/or that bring the individual into significant conflict with societal norms or authority figures. The underlying causes are various and mechanisms are poorly understood but mostly associated with the serotonin system and anxiety state.

Oppositional Defiant Disorder (ODD)

**Definition and features:** Persistent pattern of negativistic, defiant, and hostile behaviors toward adults and authorities, including arguments, temper outbursts, deliberate annoyance, and vindictiveness. It’s considered an initial, milder form of conduct disorder. Prevalence is 10% in school-age children, more common in boys before puberty and about equal after puberty.

**Etiology**

Associated causes may include family conflict, poor parenting, learning disorder, school failure, low self-esteem, mood lability, ADHD, drug abuse, and over-activity.

**Treatment**

It’s important to advise parents to spend time interacting with a child, to care and reward desired behavior and not simply punish undesired behavior, and to be consistent in parents’ words and deeds. Without special care in time, it will develop into conduct disorder.

Conduct Disorder

**Definition and features:** Conduct disorder refers to a repetitive and persistent violation in four areas (aggression, property destruction, deceitfulness/theft, and rules) lasting over 6 months in a child younger than 18 y/a. These behaviors are often referred to as “antisocial behaviors” and often seen
as the precursor to antisocial personality disorder. It is the **No.1 reason for a child or adolescent to be sent to a psychiatrist.** It affects **10%** of school children; **male:female = 9:1.** Symptoms usually gradually remit.

**Etiology**

It may include genetic factors, family stress, school environment, ADHD, mood disorder, and substance abuse (especially alcohol).

**Essentials of diagnosis**

1. The main manifestations are repetitive aggression, fighting, cruelty, property destruction, cheating, theft, robbery, and school truancy lasting over 6 months in a patient younger than 18 y/a.

2. **The major outcome or progress is “antisocial personality disorder” diagnosed when the individual with conduct disorder is over 18 y/a.**

3. The major differential diagnosis is oppositional defiant disorder.

**Treatment**

1. **Cognitive-behavioral modification is the relatively effective therapy.** It’s very important to build up healthy group identity and role models. Punishment/incarceration is often ineffective.

2. Medical therapies: Use lithium for aggressive behavior, carbamazepine for aggression with emotional lability, and haloperidol for rage and impulsion.

**Order of Progression of Associated Disorders**

ADHD → Oppositional disorder → Conduct disorder → Antisocial personality disorder → Alcoholism

**Intermittent Explosive Disorder**

It’s a disorder characterized by discrete episodes of failure to resist aggressive impulses that result in serious consequence. The aggression degree is usually out of proportion to the stressor, and tends to resolve spontaneously. Prevalence: young male > female. Associated risk factors include CNS trauma or diseases, genetics, hyper-androgen levels, bad occupational and lawful records, poor marital status, etc.

**Treatment**

Helpful therapies include psychotherapy combined with medications (antipsychotics, anticonvulsants, beta-blockers, or SSRIs).

**Kleptomania**

It’s a disorder characterized by the recurrent failure to resist impulses to steal objects with trivial values or not needed. Patient feels less anxious after the stealing but guilty or ashamed of the actions. Prevalence is female > male. Associated disorders include stress in life, mood disorder, OCD, and mild mental retardation.
Treatment

Insight-oriented therapy, behavioral therapy (aversive conditioning and systematic desensitization), or/and SSRIs may be helpful.

Pyromania

It’s a disorder characterized by deliberate fire-setting on more than one occasion. Seen more frequently in men associated with intellectual disability, alcohol abuse, and history of truancy and cruelty to animals; lack remorse for the consequences. Prevalence: male > female.

Differential diagnosis

Necessary rule-outs: arson, conduct disorder, and antisocial personality disorder.

Treatment

There is no effective treatment; incarceration may be necessary.

DEPRESSIVE DISORDERS

Disruptive Mood Dysregulation Disorder (DMDD)

DMDD is a condition in which a child is chronically irritable and experiences frequent, severe temper outbursts that are grossly out of proportion to the situation at hand. These occur, on average, ≥ 3 times each week for ≥ 1 year up to age 18 years. DMDD (previously as a bipolar disorder) is at increased risk for depression and anxiety as adults, but not adult bipolar disorder. It occurs more often in boys than girls.

Essentials of diagnosis

1. Symptoms go far beyond temper tantrums in children to temper outbursts that are grossly out of proportion in intensity to the situation, which is severe enough for clinical attention.
2. Between outbursts, children display a persistently irritable or angry mood, most of the day and nearly every day.
3. A DMDD diagnosis requires the above symptoms to be present in at least two settings (at home, at school, or with peers) for 12 or more months, and symptoms must be severe in at least one of these settings. During this period, the child must not have gone 3 or more consecutive months without symptoms. The onset of symptoms must be before age 10, and a DMDD diagnosis should not be made for the first time before age 6 or after age 18.

Treatment

Individualized medications (atypical antipsychotics), psychotherapy and a combination of the two are used as treatments.
**Major Depressive Disorder (MDD)**

It is also called Major Depression or Unipolar Depression, including single and recurrent episodes, defined as depressed mood or anhedonia (loss of pleasure or interest) more than 2 week’s course that changes from the patient’s previous level of functioning. The course is mostly between 2 weeks and 2 years. Prevalence is 15-25%; female:male = 2:1. Onset is usually 20-40 y/a. Suicide mortality is 10-15%. Subclasses are Single Episode and Recurrent MDD. The prognosis is better than other mood disorders if treated properly, and is worse if psychotic symptoms are present.

**Etiology**

Studies have shown that depression is influenced by both biological and environmental factors – associated with genetics (first degree relatives of patients with higher risk), low levels of serotonin (5-HT) and norepinephrine (NE), abnormal dopamine (DA), sex hormone imbalances, chronic diseases, stress (divorce, job loss), and loneliness.

**Essentials of diagnosis**

1. DSM-5 criteria: ≥ five of the following symptoms must have been present for 2 weeks: (1) Depressed mood (feeling sadness or emptiness) most of the day and nearly every day; (2) Loss of energy, anhedonia, or fatigue most of the day; (3) Reduced interest in activities that used to be enjoyed, sleep disturbances (insomnia or hypersomnia); (4) Difficulty concentrating, memorizing, or making decisions; (5) Feelings of worthlessness or guilt and recurrent suicide thoughts or intentions; (6) Others: psychomotor agitation or retardation; significant weight loss or gain. (7) Absence of a manic or hypomanic episode.

2. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

3. The episode is not attributable to the physiological effects of a substance/drug or to another medical condition (hypothyroidism, chronic fatigue syndrome, etc), and is not better explained by other psychotic disorders.

4. P/E is usually normal but dexamethasone suppression test or thyrotropin-releasing hormone test is abnormal.

**Differential diagnosis**

Dysthymia (with milder symptoms lasting more than 2 years); normal grief; drug abuse; drug effects; hypothyroidism; Parkinson disease; dementia; postpartum depression/Blues/psychosis, etc.

**Postpartum Blues (“Baby Blues”):**

Mild depression sometimes occurs immediately after birth and lasts up to 2 weeks. Mother may have sadness, mood lability, and tearfulness, but cares about the baby. It’s self-limited and no treatment is necessary.

**Postpartum depression:**

Typical depressed symptoms usually occur within 1-3 month after birth (mostly the 2nd baby) and symptoms may continue more than 1 month. Patient usually has depressed mood, excessive anxiety, sleep
disturbances, and weight changes. The mother may have negative thoughts of hurting the baby. Treat the patient with antidepressants.

Postpartum psychosis:

Severe depression and psychosis may occur 2-3 weeks after the first birth and may continue. Patient usually has depression and delusion, and may have thoughts of hurting the baby. Treat with antidepressants and mood stabilizers or antipsychotics.

Normal grief:

Also known as Bereavement, it usually begins after the death of a loved one, presenting with feelings of sadness, tearfulness, worrying about the deceased, irritability, disturbed sleep, and poor concentration. It typically lasts < 6 months and only needs supportive care (psychotherapy).

Treatment

1. Cognitive psychotherapy is the initial treatment, which will help change the patient’s distorted thoughts about self, future, and the world, and help the patient deal with conflicts, stress, sense of loss, etc. Combined with an SSRI, it will be the most effective treatment. Patient must first be protected from suicide.

2. Pharmacotherapy -- requires 3-4 weeks for initial effects and 6 months for maintenance.

   (1) SSRIs (Selective serotonin reuptake inhibitor, increasing 5-HT):

   They are the 1st line medications for both depression and anxiety disorder. With low toxicity but more sexual S/E, CNS and GI toxicity; avoid use with MAOIs (Serotonin syndrome: fever, CVS collapse), avoid TCAs. Fluoxetine—most commonly used; sertraline—safe with CVD; paroxetine—good with compulsive and panic disorder; newer and stronger: citalopram and escitalopram.

   (2) TCAs (Tricyclic antidepressants, increasing 5-HT and NE):

   They are the 2nd line drugs for depression, anxiety, chronic pain (amitriptyline), and enuresis (imipramine). Among them, nortriptyline has sedation while desipramine has not. This group of drugs has low cost but significant side effects --Cardiac arrhythmias, anticholinergic effects, orthostatic hypotension, sexual dysfunction, and seizures.

   (3) MAOIs (Monoamine oxidase inhibitor, increasing NE):

   Phenelzine and tranylcypromine are used mostly. It’s the best treatment for atypical depression with brief psychosis, phobia, hypersomnolence, or hyperphagia. It requires dietary restrictions (avoid cheese, red wine, and anti-cough agents) to avoid serious “hypertensive crisis”. Other S/E: Sexual dysfunction, orthostatic hypotension, weight gain, and sleep disorder.

   (4) Heterocyclics: 2nd and 3rd-generation antidepressants with varied actions, better for atypical depression.

   Bupropion—increasing both DA and NE; best for depression with ADHD, alcohol/smoking cessation, or confusion; with risk of seizure but least S/E on sexual function.

   Trazodone—inhibiting 5-HT reuptake, good choice for depression with sleep disorder; S/E: may cause priapism.
3. **ECT (Electroconvulsive therapy):**

Indicated in patients with serious **suicidal ideas** or side effects of medication. It’s also safe in the 1st trimester pregnancy. Adverse effects include headaches, transient memory loss, and posterior shoulder dislocation (rare).

**Persistent Depressive Disorder -- Dysthymia**

**Definition and diagnosis:** A chronic disorder characterized by a depressed mood lasting most of the time during the day and most of the days in a week but milder than major depression for **more than 2 years** (In DSM-4, it’s “Chronic major depression”).

**Risk factors:** More common in females with low social-economic status (SES). Most patients have other psychiatric disorders such as anxiety, substance abuse or borderline personality disorder.

**Treatment**

2. Antidepressant therapy: If the above therapy fails, an SSRI can be used.

**Differential diagnosis:** Same as for major depression.

**Atypical Depression**

It is characterized by reverse vegetative changes such as increased sleep, appetite, and weight. Depressed mood tends to be worse in the evening. Patient complains of “feeling heavy.” Atypical depression is more common in females and in individuals with bipolar I, bipolar II disorder, major depressive disorder, and “seasonal affective disorder”. Depressive episodes in bipolar disorder tend to have atypical features, as does depression with seasonal patterns.

**Treatment**

Lifestyle modification plus medications are helpful. An SSRI (with less S/E) is first chosen; if it’s not satisfactory, a MAOI is chosen.

**Premenstrual dysphoric disorder (PMDD)**

PMDD is a condition in which a woman has severe depression symptoms, irritability, and tension before menstruation. The symptoms of PMDD are more severe than those seen with premenstrual syndrome (PMS, emotional symptoms +/- physical symptoms), occurring in 3-8% of women with menstruations.

**Etiology**

The causes of PMS and PMDD are unclear. They may be associated with the lack of serotonin and mediated by the fluctuations of the levels of sex hormones in the luteal phase of the menstrual cycle.

**Essentials of diagnosis**
1. Anxiety (feelings of tension or anxiety, panic attacks), severe depression (feelings of sadness or despair, mood swings, lasting irritability, lack of interest in daily activities, difficulty focusing, thoughts of suicide), seasonal affective disorder (SAD), and eating/sleeping disorder.

2. Physical symptoms, such as bloating, breast tenderness, headaches, and joint or muscle pain.

3. The presentations occur during the week before menstruation, and go away once it starts. A diagnosis of PMDD requires the presence of at least five of the above symptoms.

**Treatment**

1. The goal is to reduce the patient’s suffering and the disruption to their social relationships. **SSRIs** are used as the first-line therapy. **L-tryptophan**, a serotonin precursor, is also helpful with symptoms.

2. Hormonal birth control containing drospirenone and low levels of estrogen helps relieve severe PMDD symptoms.

3. Lifestyle changes such as regular exercise and a well-balanced diet may be helpful.

**Seasonal Pattern Specifier for Mood Disorders**

Formerly known as **Seasonal Affective Disorder (SAD)** or seasonal depression, is characterized by seasonal, recurrent major depressive disorder that occurs at a specific time of the year (mostly during autumn and winter) and fully remits otherwise. Lethargy and increased weight and sleep may be present. In DSM-5, it is no longer classified as a unique mood disorder, but a “Seasonal Pattern Specifier”.

**Treatment**

Phototherapy and antidepressive (bupropion) are helpful.

**Mix: Serotonin Syndrome**

This is a potentially **life-threatening** condition occurring during therapeutic use of SSRIs, usually with inadvertent interactions between medications or abused substances with serotonic nature.

**Common manifestations**

3. Somatic effects: tremors, myoclonus, etc.

**Treatment**

1. Stop the SSRI.
2. Symptomatic treatment of fever, tachycardia, hypertension, diarrhea, etc.
3. Use serotonin antagonist—cyproheptadine if necessary.
BIPOLAR AND RELATED DISORDERS

Definition: Bipolar disorder is a mood disorder that is characterized by episodes of mania, hypomania, and major depression causing significant functional impairment. The onset age is about 30. Prevalence is 1-4% for both males and females. The subtypes include bipolar I and bipolar II.

Subtypes
1. Bipolar I: More than one manic episode or mixed depressive-manic episode.
2. Bipolar II: More than one major depressive and one hypomanic episode. This type does not meet the criteria for full manic or mixed depressive-manic episodes.
3. Other subtypes may include (1) Rapid cycling type: more than four episodes (major depressive, manic, mixed, or hypomanic episode) in 1 year; (2) Cyclothymic type: chronic and less severe, with alternating periods of hypomania and moderate depression for more than 2 years.

Etiology
Unknown. It’s more prevalent among high-income and low-education population and has a strong genetic component. It may coexist with anxiety, alcohol dependence, and substance abuse. Suicide mortality is up to 10%.

Essentials of diagnosis
1. Patient usually has persistently elevated, expansive mood lasting longer than 1 week--increased self-esteem or grandiosity, sexual activity, and distractibility; excessive goal-directed activities and talkativeness (pressured speech); decreased need for sleep; flight of ideas; psychomotor agitation.
2. P/E results are mostly normal. Diagnosis is made based on the above symptoms and by excluding other relevant disorders and drug effects (e.g., using an antidepressant may trigger manic episode).

Differential diagnosis
Schizophrenia; personality disorders; hyperthyroidism; drug effects.

Treatment
1. Acute mania: Hospitalize the patient who is usually a risk to self and others. Treat the patient with mood stabilizers--lithium is still the drug of choice in both acute phase and maintenance. It takes 2-4 weeks to be fully effective and is tapered off in 1 year. If unresponsive, valproic acid is used (first-line effective medicine after lithium in acute mania), and carbamazepine or lamotrigine is used as 2nd line of drugs. Antipsychotics (haloperidol) are used in severe psychic or refractory agitation due to shorter onset of action.
2. Bipolar depression: Mood stabilizers should be used first to avoid inducing mania; antidepressants may be added but not alone. ECT is only indicated for refractory cases.
3. Combined psychotherapy is helpful.

Table 16-1: Major Indications and Adverse Effects (S/E) of Mood Stabilizers
Valproic acid  **Indications:** Acute mania, bipolar disorder; convulsion.  **S/E:** GI toxicity, tremor, sedation, alopecia, and weight gain; rarely, pancreatitis, hepatotoxicity, thrombocytopenia, agranulocytosis.

Lithium  **Indications:** Acute mania (No.1 and maintenance therapy); bipolar disorder (prophylaxis).  **S/E:** Thirst, polyuria, diabetes insipidus, hypothyroidism, GI, teratogenicity, tremor, ataxia, delirium, seizure. Avoid use if renal function is impaired.

Carbamazepine  **Indications:** 2nd-line for bipolar disorder; convulsion; peripheral neuralgia.  **S/E:** Skin rash, cardiac A-V block, leukopenia; rarely, aplastic anemia or Stevens-Johnson syndrome.

Lamotrigine  **Indications:** 2nd-line for bipolar disorder; convulsion; peripheral neuralgia.  **S/E:** Blurred vision, GI, Stevens-Johnson syndrome.

**Cyclothymic Disorder**

**Definition and diagnosis:** It’s a chronic disorder characterized by many periods of depressed mood and hypomanic mood for more than 2 years. It’s considered a milder form of bipolar II disorder.

**Risk factors:** More frequent in females and in association with bipolar disorder, borderline personality disorder, substance abuse, and marriage problems.

**Treatment**

1. Antimanic drugs (lithium, valproic acid, or carbamazepine) are usually the drugs of choice.

2. Psychotherapy can help patient gain insight into their illness and how to cope with it.

**Differential diagnosis**

Substance abuse; bipolar disorder; personality disorder.

**NEUROTIC, STRESS-RELATED AND SOMATOFORM DISORDERS**

**ANXIETY DISORDERS**

It’s a group of psychological and physiological disorders characterized by excessive worries, hypervigilance, fears, restlessness, difficulty concentrating, and sleep disturbance; may be accompanied with autonomic hyperactivity and motor tension. Anxiety disorders cover several different forms of abnormal and pathological fear and anxiety, including generalized anxiety, phobic, panic disorders, Obsessive-compulsive disorder (OCD), acute stress disorder, and post-traumatic stress disorder (PTSD). Each of them has its own characteristics and symptoms and requires different treatment.

**Etiology**

1. Psychodynamic theory: Anxiety occurs when instinctual drives are thwarted.

2. Behavioral theory: Anxiety is a conditioned response to environmental stimuli originally paired with a feared situation.
3. Biologic theory: Various neurotransmitters (especially GABA, NE, and 5-HT) and various CNS structures (especially reticular activating system and limbic system) may be involved.

### Generalized Anxiety Disorder

It’s defined as excessive, poorly controlled anxiety about events or activities in life that causes significant impairment or distress for > 6 months; usually with both psychological and somatic symptoms (fatigue, restlessness, irritability, insomnia, muscle tension, etc).

#### Risk factors

There may be a genetic predisposition for an anxiety trait. Prevalence is male:female = 1:2. Associated disorders include depression, somatic symptoms, and substance abuse.

#### Treatment

1. Lifestyle changes and behavioral psychotherapy (relaxation training and biofeedback) are beneficial.
2. Medicine (SSRIs, venlafaxine, buspirone) are commonly used with good effects.

Benzodiazepines (BZ) are used for immediate relief of acute symptoms but long-term use should be avoided for risk of dependence. Other adverse effects: sedation, confusion, memory deficits, and respiratory depression.

**Benzodiazepines (BZs) include:** diazepam, lorazepam (IV use for emergencies), clonazepam (longer half-life, less addiction risk), alprazolam (more use in panic disorder), oxazepam and chlordiazepoxide (more use in alcohol withdrawal), temazepam, flurazepam.

**Flumazenil:** a benzodiazepine antagonist that is used only in acute BZ overdose and not in chronic dependence (may cause tremor or seizures similar to delirium tremens).

### Panic Attack and Panic Disorder

Panic disorder is recurrent, unexpected panic attacks—intense anxiety accompanied with marked physical symptoms such as tachycardia, hyperventilation, dizziness, and sweating. Panic attacks usually last for a few min. The disorder is associated with agoraphobia, depression, generalized anxiety, and substance abuse. The prevalence is male:female = 1:2.

#### Risk factors

Possibly include genetic factors, separations during childhood and interpersonal loss in adulthood. Most patients have panic symptoms in response to “panicogens” (lactate, CO2, yohimbine).

#### Treatment

1. 1st line drug: **Paroxetine, fluoxetine**, alprazolam. Clonazepam (BZ) is only used for immediate symptomatic relief.
2. Cognitive-behavioral therapies (CBT): Relaxation training for panic attacks and systematic desensitization for agoraphobic symptom are both effective.
Phobic (Anxiety) Disorder

It’s defined as irrational fear and avoidance of objects and situations. Subtypes include:

1. **Agoraphobia**: Fear or avoidance of places from which escape would be difficult in the event of panic conditions (public places, crowds, outside alone, etc). It occurs more in females and often leads to severe restrictions on the individual’s travel and daily routine.

2. **Social phobia**: Fear of humiliation or embarrassment in either general or specific social situations (e.g., at public speaking, “stage fright”).

3. **Specific phobia**: Fear or avoidance of objects or situations other than agoraphobia or social phobia, such as animals or insects, natural environments (e.g., storms), injury (e.g., injections, blood), and situations (e.g., heights, darkness).

Treatment

1. **CBT**: Very effective for phobia, combined with systematic desensitization and assertiveness training.

2. Pharmacotherapy: SSRIs or BZ is effective for social phobias, and beta-R blockers are best for performance anxiety (“stage fright”).

Separation Anxiety Disorder (SAD)

**Definition and diagnosis**: It is an anxiety disorder among children in which the child experiences excessive anxiety, fear and distress regarding separation from home or from people to whom the individual has a strong emotional attachment (e.g. a parent). Major presentations include inappropriate anxiety, clinging to the parent, crying, throwing tantrums, fear of harm, and difficulties sleeping. SAD can also cause significant negative effects within a child’s everyday life. Symptoms must persist for at least four weeks and must be present before a child is 18 years of age to be diagnosed. Etiology is unknown.

Treatment

Behavioral, cognitive and individual psychotherapies are helpful. When these are failed in extreme cases, SSRIs can be used.

Selective Mutism (SM)

**Definition and diagnosis**: SM is an anxiety disorder in which a person who is normally capable of speech consistently fails to speak in specific social situations or to specific people, mostly in children. Children with SM stay silent even when the consequences of their silence include shame, social ostracism, or even punishment. Symptoms must persist for at least 1 month to be diagnosed. SM usually co-exists with shyness or social anxiety. Etiology is unknown.

Treatment
Self-modelling, mystery motivators, stimulus fading, desensitization, shaping, spacing and antidepressive (SSRIs) may be helpful. SM does not necessarily improve with age. Treat early to avoid chronic depression.

**Mixed Anxiety and Depressive Disorder**

This category should be used when symptoms of anxiety and depression are both present, but neither is clearly predominant, and neither type of symptom is present to the extent that justifies a diagnosis if considered separately. When both anxiety and depressive symptoms are present and severe enough to justify individual diagnoses, both diagnoses should be recorded and this category should not be used.

**OBSESSIVE-COMPULSIVE AND RELATED DISORDERS**

**Obsessive-Compulsive Disorder (OCD)**

OCD is characterized by recurrent obsessions or/and compulsions that are recognized by the individual as unreasonable, affecting the individual’s level of functioning. Obsessions are persistent, unwanted, intrusive, and anxiety-provoking thoughts or impulses, commonly concerning contamination, doubt, guilt, aggression, and sex. Compulsions are peculiar behaviors to reduce anxiety, commonly hand-washing, checking, and counting.

**Etiology**

It may be associated with 5-HT metabolism, genetics, depression, and other psychiatric disorders. Onset is insidious during childhood or early adulthood.

**Diagnosis**

OCD is diagnosed by recurrent, unreasonable obsessions or/and compulsions, occurring more frequently among young people, with similar incidence in male and female. It may coexist with Tourette disorder.

**Treatment**

1. **CBT**: Exposure and desensitisation relaxation training, response prevention, thought-stopping techniques, and modelling. Patient education and counselling are highly important.

2. Medications: An SSRI (paroxetine, fluoxetine, sertraline, or fluvoxamine) is the first-line medicine. Higher doses of SSRIs or clomipramine are more effective for OCD.

**Table 16-2: The Difference between Obsession and Compulsion**

<table>
<thead>
<tr>
<th>Obsession</th>
<th>Intrusive, senseless, and distressing thoughts that increase patient’s anxiety. E.g., fear of contamination.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compulsion</td>
<td>Rituals, such as recurrent counting and checking, that are done to neutralize thoughts; time-consuming and tend to lower anxiety.</td>
</tr>
</tbody>
</table>
Body Dysmorphic Disorder

**Definition and diagnosis:** A disorder characterized by the patient’s **irrational belief that some body part is abnormal**, defective, or misshapen despite constant reassurance. The disorder causes the patient’s functional level impaired. The patient’s most common concern is for facial flaws, with constant mirror-checking, attempts to hide the claimed deformity and avoidance of social activities. It’s more common in adolescent and young females, who are difficult to get married or keep the marriage. It may be Assoc/w 5-HT system abnormalities, depressive disorder, anxiety disorder, and OCD.

**Treatment**

Individual psychotherapy to help the patient deal with stress of claimed deformity. If persistent, antidepressants (SSRIs) may help.

Hoarding Disorder (HD)

HD is a pattern of behavior that is characterized by the excessive acquisition of and inability or unwillingness to discard large quantities of low-value objects that cover the living areas of the home and cause significant distress or impairment. Compulsive hoarding behavior has been associated with health risks, impaired functioning, economic burden, and adverse effects on friends and family members.

**Treatment:** No effective treatment is available.

Trichotillomania (Hair-Pulling Disorder)

It’s a disorder characterized by recurrent, uncontrolled pulling of one’s own hair, resulting in significant hair loss. Prevalence is female > male. Associated disorders include OCD, depression, etc.

**Treatment**

Use behavior-modification techniques to decrease patient’s anxiety, along with SSRIs.

Excoriation (Skin-Picking) Disorder

Also known as dermatillomania, compulsive skin picking, etc, it is an impulse control disorder characterized by the repeated urge to pick at one’s own skin, often to the extent that damage is caused. Research has suggested that the urge to pick is similar to an OCD but others have argued that the condition is more akin to substance abuse disorder.

**Treatment**

The two main therapeutic strategies are pharmacological (SSRIs; opioid antagonists; glutamatergic agents) and behavioral intervention.
TRAUMA- AND STRESSOR-RELATED DISORDERS

Acute Stress Disorder (ASD) and Post-traumatic Stress Disorder (PTSD)

Definition and diagnosis

1. Both hold these characteristics:

   (1) Re-experiencing the overwhelming traumatic event or stressor (nightmare, flashbacks of war, rape, or disaster experience) to which the individual reacts with fear and helplessness. Patients continuously relive the event and avoid anything that reminds them of the event. Symptoms adversely affect the individual’s level of functioning.

   (2) Increased arousal (anxiety, sleep disturbances, hypervigilance, or impulsivity), “survivor guilt”, depression, or feelings of fear or helplessness.

   (3) Avoidance of stimuli associated with the trauma, or numbing of responsiveness.

   (4) Etiology: Stressors usually precipitate ASD. Traumatic events (sexual assault, warfare, serious injury) usually precipitate PTSD.

2. Differentiation: When post-stressor symptoms last from 2 days to 30 days, it is defined as ASD. When post-traumatic symptoms last more than 4 weeks (1 mo), it is PTSD. Symptoms usually begin immediately after trauma, but may also occur after months or years. Depression and substance abuse must be ruled out because both of them worsen the diagnosis.

   Treatment

1. Psychological counselling after a stressful event may prevent PTSD from developing. Supportive group psychotherapy with other survivors, relaxation techniques and hypnosis are all helpful.

2. Medical therapies for resistant cases: SSRI is the first line of drug; TCA or MAOI is the second.

Adjustment Disorder

Definition and diagnosis

Maladaptive reactions to an identifiable psychosocial stressor that occur within 3 months of the stressor and last 1-6 months. It’s very common in all age groups and associated with social and occupational malperformance, erratic or withdrawn behavior.

   Treatment

   Remove the stressor and use brief psychotherapy to improve adjustment skills. If severe, an anxiolytic or antidepressant can be used to alleviate symptoms.

Differential diagnosis

ASD; PTSD; generalized anxiety disorder.
Reactive Attachment Disorder (RAD)

Definition and diagnosis

RAD is an uncommon disorder in children characterized by markedly disturbed and developmentally inappropriate ways of relating socially in most contexts. It can take the form of a persistent failure to initiate or respond to most social interactions in a developmentally appropriate way—known as the “inhibited form”.

Clinical features--The disorder can manifest itself in two ways:
1. Indiscriminate and excessive attempts to receive comfort and affection from any available adult, even relative strangers.
2. Extreme reluctance to initiate or accept comfort and affection, even from familiar adults, especially when distressed.

Treatment

Management may include psychosocial support services for the family unit (including financial or domestic aid), psychotherapeutic interventions, education (basic parenting skills and child development), and monitoring of the child’s safety within the family.

Disinhibited Social Engagement Disorder (DSED)

Definition and diagnosis

DSED or Disinhibited Attachment Disorder of Childhood is an attachment disorder that consists of “a pattern of behavior in which a child actively approaches and interacts with unfamiliar adults.” and which “significantly impairs young children’s abilities to relate interpersonally to adults and peers.” For example, sitting on the lap of a stranger or peer, or leaving with a stranger.

DSED is not diagnosed before the age of 9 months or after 5 y/a. Risk factors include inconsistent or insufficient care from a primary caregiver.

Treatment

Two effective treatment approaches are play therapy and expressive therapy, which help form attachment through multi-sensory means.

PERSONALITY DISORDERS

(ICD-10: DISORDERS OF ADULT PERSONALITY AND BEHAVIOR)

Definition and features: These are disorders of personality patterns that are pervasive, inflexible, and maladaptive causing impaired social-behavioral functions. They are a group of common psychiatric disorders that lack proper care. They can be classified into three clusters (“3 Ws”: A-Weird, B--Wild, C--Worried). General features include: (1) Long history dating back to childhood; (2) Recurrent maladaptive behavior and major difficulties with interpersonal relationships or society; (3) Low
self-esteem and lack of confidence; (4) Minimal introspective ability with a tendency to blame others for all problems; (5) Depression with anxiety when maladaptive behavior fails.

**Etiology:** Unknown. It may be associated with genetic factors, “original family”, and childhood experiences.

**Prevalence:** More males have antisocial and narcissistic personality disorders, and more females have borderline and histrionic personality disorders.

**Onset:** Late adolescence or early adulthood.

**Course:** It’s usually chronic over decades and very difficult to treat because the patient is not willing to seek treatment. Mostly symptoms of paranoid, schizoid, and narcissistic personality disorder worsen with age, whereas symptoms of antisocial and borderline personality disorder usually ameliorate.

**Principles of treatment:** Psychotherapy is the mainstay of therapies, mostly long-term, intensive psychodynamic and cognitive therapy.

### Specific Types and Clinical Features

#### I. Cluster A Personality Disorders—“Weird”

Peculiar thought processes and inappropriate affect.

**Paranoid personality disorder**

Pervasively distrustful/mistrustful, suspicious, taking other’s motivation as malevolent, socially isolated, and emotionally cold.

**Schizoid personality disorder**

Socially isolated “loners” with restricted and distant emotions and friendship; disinterested in others and indifferent to joy, praise, or criticism.

**Schizotypal personality disorder**

Odd thought, behavior, appearance, and perceptions; socially isolated and uncomfortable with others. It’s differentiated from schizoid personality disorder by magical/weird thinking and affect, ideas of reference and persecution, and brief psychotic episodes.

**Clinical strategy for Cluster A**

Patients are suspicious and distrustful of physicians and rarely seek treatment. Therapists should be clear, honest, non-controlling and non-defensive. Maintain emotional distance and avoid humor.

#### II. Cluster B Personality Disorders—“Wild”

Mood lability, dissociative symptoms, and preoccupation with rejection.

**Histrionic personality disorder**
Colorful, exaggerated behavior, emotions and appearance to draw attention (over self-centered; theatrical and sexually seductive. It’s mostly seen in female.

Borderline personality disorder

Unstable affect, mood, relationships, and self-image; chronic feelings of emptiness, impulsivity, recurrent suicidal behaviors, and inappropriate anger. Psychotic symptoms may be present with stress. The main defense mechanism is splitting.

Antisocial Personality Disorder (ASPD)

Definition and diagnosis: A pervasive personality pattern of disregard for, or violation of, the rights of others; with continuous antisocial or criminal acts, inability to conform to social rules, marked impulsivity, violation of the rights of others, deceitfulness, and lack of remorse. There may be a history of crime, legal problems, and impulsive and aggressive behavior. It usually starts around 15 y/a as conduct disorder and is diagnosed after the age 18.

Etiology: It may include hormones and neurotransmitters (high testosterone, low 5-HT), limbic neural maldevelopment, head trauma, cultural influences, and environment.

Treatment: ASPD is considered to be among the most difficult personality disorders to treat. Because of their very low or absent capacity for remorse, patients often lack sufficient motivation and fail to see the costs associated with antisocial acts. Therapeutic techniques should be focused on rational and utilitarian arguments against repeating past mistakes.

Narcissistic personality disorder

Sense of self-importance, grandiosity, and entitlement; in need of admiration and lack of empathy; jealousy and improper rage with criticism. It occurs mostly in low-educated patients.

Clinical strategy for Cluster B

Patient is manipulative and demanding (attention), and tends to change the rules. Therapists should be firm (stick to the treatment plan), fair (not punitive or derogatory), and consistent in rules.

III. Cluster C Personality Disorders —“Worried”

Anxiety; preoccupation with criticism or rigidity.

Avoidant personality disorder

Socially inhibited, feeling inadequate, shy and lonely, and hypersensitivity to criticism; preoccupied with rejection; unwilling to get involved with people.

Dependent personality disorder

Submissive and clinging, feeling inadequate and helpless; avoiding responsibility and making decisions; always in need of care.

Obsessive-compulsive personality disorder
Preoccupied with details, orderliness, perfectionism, and control; often consumed by the details of everything and lose the efficiency (goals); inflexible morals and values. It’s different from obsessive compulsive disorder (OCD).

Clinical strategy for Cluster C

Patients are worried but controlling, and their words may be inconsistent with actions. These may ruin the treatment. Therapists should give clear recommendations, but not force the patient into decision. Be caring, sympathetic, and patient.

SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDERS

Schizophrenia

Definition: It is a mental disorder characterized by a disintegration of the process of thinking and of emotional responsiveness, which impairs judgment, behavior, and ability to interpret reality. It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of around 1.5%. Symptoms must be present for more than 6 months to make the diagnosis. The incidence is higher in males and the onset is earlier in males (male: 20’s y/a, female: 30’s y/a). Suicidal rate is about 10%.

Etiology and risk factors

1. Unknown; associated with high levels of dopamine (DA) and abnormal 5-HT in the brain.

2. Strong genetic trend or family history: General prevalence is 1%; monozygotic twin is 47%; dizygotic twin, first-degree relative, and one schizophrenic parent are all about 12%; patient with two schizophrenic parents has 40% of prevalence.

3. Environment: More prevalent in patients with low social-economic status (SES), a conflicting environment, and a birth season in the winter and early spring (may include viral infection). If family members are critical, intrusive, and hostile to the patient, the relapse rate is high. If family members are supportive, understanding, and loving, the relapse rate is low.

Essentials of diagnosis

1. More than two of the following characteristic psychotic symptoms affecting social or occupational functions for at least 6 months:

   (1) Positive symptoms: Delusions (mostly bizarre), hallucinations (mostly auditory), disorganized speech, and disorganized or catatonic behaviour.

   (2) Negative symptoms: Flat affect, poverty of speech, decreased emotional reactivity, and anhedonia.

2. P/E: Usually normal, but may show saccadic eye movements, hypervigilance, etc.

3. Brain imaging: CT and MRI usually reveal lateral and third ventricular enlargement, reduction in cortical volume (associated with negative symptoms and neuro-psychiatric impairment).
PET: May show hypoactivity of the frontal lobes and hyperactivity of the basal ganglia relative to the cerebral cortex.

4. Psychological Tests:
   (1) IQ tests-- lower on all IQ tests.
   (2) Neuropsychological tests: Usually are consistent with bilateral frontal and temporal lobe dysfunction (deficits in attention, retention time, and problem-solving ability).
   (3) Personality tests: May show bizarre ideations, etc.

**Differentiation**

**Catatonia:**

Catatonia is a state of neurogenic motor immobility and behavioral abnormality manifested by stupor. It is not a separate disorder, but is associated with psychiatric conditions such as schizophrenia (catatonic type), bipolar disorder, post-traumatic stress disorder, depression and other mental disorders, as well as drug abuse or overdose (or both). It may also be seen in many medical disorders including CNS infections, autoimmune disorders, focal neurologic lesions, metabolic disturbances, and alcohol or benzodiazepine (BZ) withdrawal. **Treatment: BZ is the first-line option.** Electro-convulsive therapy is sometimes effective. NMDA antagonists can be tried for BZ resistant catatonia.

**Treatment**

1. Hospitalization is recommended to make patient safe and stabilized. Supportive psychotherapy mainly aims at building up a relationship of mutual trust and understanding between the patient and physician.

2. **Antipsychotics**

   (1) **Typical:** Blocking DA-R (D2, D4 subtypes). Indicated for psychotic disorders, acute agitation or mania, and Tourette syndrome.

   **High-potency:** Haloperidol, droperidol, fluphenazine, and thiothixene.

   **Adverse effects of typical antipsychotics:**
   
   (a) More extrapyramidal symptoms (EPS): acute dystonia or dyskinesias (pseudo-parkinsonism, tremor, and rigidity)-- treated with **bentropine, amantadine** or diphenhydramine; akathisia-- treated with propranolol or BZ.

   (b) **Tardive dyskinesia** (lip smacking, etc) -- It’s treated by changing to clozapine or risperidone, no anticholinergics.

   (c) **Neuroleptic malignant syndrome:** fever, rigidity, and autonomic instability (instable HR, BP and conscious status). **Treatment:** Stop neuroleptic; give **dantrolene or bromocriptine** along with IV fluid.

   (d) Hyperprolactinemia: amenorrhea, gynecomastia, and galactorrhea. Treatment depends on specific cases.

   **Low-potency:** Thioridazine (S/E: retinal pigmentation), **chlorpromazine** (with more anticholinergic S/E: dry mouth, orthostatic hypotension, constipation, and urine-retention).
(2) **Atypical**: Blocking DA₂-R and 5HT₂-R. Clozapine and olanzapine are effective for negative symptoms; risperidone is effective for both positive and negative symptoms. Similar new medicines: quetiapine, ziprasidone, aripiprazole. Currently these are the 1\textsuperscript{st}-line medicines for schizophrenia, with fewer EPS and anticholinergic S/E.

**Note**: Clozapine is best reserved for patients who have no response to adequate therapies of typical and atypical antipsychotics, and who have severe negative symptoms and tardive dyskinesia. It is never used as a first-line therapy.

**Adverse effects of atypical antipsychotics:**

- **Clozapine**—the main adverse effect is agranulocytosis and thus weekly CBC testing is necessary.
- **Olanzapine**—higher incidence of diabetes and weight gain; avoid in diabetic and obese patients.
- **Risperidone**—higher incidence of movement disorder; quetiapine has less.
- **Ziprasidone**—higher incidence of prolonged QT interval; avoid in patients with conduction defects.

**Specific sub-types of schizophrenia dropped by DSM-5**

Paranoid, disorganized, catatonic, residual, and undifferentiated types.

**ICD-10 defined two additional subtypes**

- **Post-schizophrenic depression**: A depressive episode arising in the aftermath of a schizophrenic illness where some low-level schizophrenic symptoms may still be present.
- **Simple schizophrenia**: Insidious and progressive development of prominent negative symptoms with no history of psychotic episodes.

### Other Psychotic Disorders

**Schizophreniform Disorder**

It’s defined as **psychotic symptoms** (hallucinations, delusions, disorganized speech or behaviour, affective or negative symptoms, and impaired social function, etc) for **more than 1 month but less than 6 months**. Most patients can return to their functional level at baseline after treatment. Be watchful that depressive suicide is a risk factor after the psychotic symptoms resolve.

**Treatment**

1. Physician must first evaluate if it’s necessary to hospitalize the patient for safety purpose.

2. Antipsychotic medicine is indicated for a 3-6 month course. Individual psychotherapy may help the patient assimilate the psychotic experience into real life.

**Schizoaffective Disorder**

It’s defined as complex symptoms of **major depressive-manic episodes and schizophrenia** (delusions or hallucinations) for **more than 2 weeks**. The prognosis is better than that for schizophrenia, but worse than that for affective disorder.
Treatment

1. Physician must first evaluate the necessity of the patient’s hospitalization for safety purpose.
2. Use an antidepressant with or without anticonvulsant to control the mood symptoms. If not effective, use antipsychotics to help control the symptoms.

(Persistent) Delusional Disorder

It’s defined as non-bizarre delusions more than 1 month and no impairment in level of functioning. Specific features and types include erotomaniac, jealous, grandiose, somatic, mixed, and unspecified. For example, the patient may believe the government will collapse soon and the leader will be replaced by him/her, but the patient still follows the law and goes to work.

Risk factors: More commonly in low SES, married, employed women.

Treatment

1. Outpatient treatment is preferred: Individual psychotherapy focusing on helping the patient understand how the delusions are distressing and interfere with normal life.
2. Antipsychotics may have limited effects.

Brief Psychotic Disorder

It’s defined as sudden onset of psychosis lasting for a few days to a month and returning to a normal premorbid functional level in a month.

Risk factors: More common in the low SES and in those with pre-existing personality disorders or psychological stressors.

Treatment

1. Physician must first evaluate the necessity of the patient’s hospitalization for safety purpose.
2. Antipsychotics and BZ can be used for short-term treatment of psychotic symptoms.

Differential diagnosis

Pay special attention to the duration of psychotic symptoms, which is key to the differentiation of brief psychotic disorder (1 day—1 month), schizophreniform disorder (1 month—6 months), and schizophrenia (more than 6 months).

Schizotypal (Personality) disorder (STPD)

It’s a disorder characterized by eccentric behavior and anomalies of thinking and affect which resemble those seen in schizophrenia, though no definite schizophrenic anomalies occur at any stage. The symptoms may include a cold or inappropriate affect; anhedonia; odd behavior; social withdrawal tendency; paranoid or bizarre ideas not amounting to true delusions; obsessive ruminations; thought and perceptual disturbances; occasional transient psychotic episodes with intense illusions, auditory or other
hallucinations, and delusion-like ideas, usually occurring without external provocation. There is no definite onset, and evolution and course are usually those of a personality disorder.

**Treatment**

STPD is among the most difficult psychotic and personality disorders to treat because people with STPD usually consider themselves to be simply eccentric, creative, or nonconformist. When patient’s social maladaptation is significant, psychotherapy and antipsychotics should be used.

**DISSOCIATIVE DISORDERS**

**Definition:** Dissociation is the fragmentation or separation of aspects of consciousness, including memory, identity, and perception. Some degree of conscious dissociation is normal, but if it’s too fragmented, it may be a pathologic dissociative disorder that interferes with patient’s normal adaptive ability.

**Dissociative Amnesia**

It refers to significant episodes in which the individual is unable to recall general or important events, usually during emotional or psychological stress. It’s more common in young women.

**Treatment**

1. First evaluate and exclude general medical conditions (head trauma, seizures, stroke, substance abuse, etc).
2. Psychotherapy may help resolve underlying emotional stress.

**Differentiation**

**Fugue state (Dissociative fugue or psychogenic fugue):**

Sudden, unexpected travel; unable to remember one’s past and confused about personal identity; usually following a stressful life event, mood disorder, or substance abuse. Most episodes are isolated and with rapid resolution, but amnesia may persist for months. **Treatment:** Same as for dissociative amnesia.

**Dissociative Identity Disorder (Multiple Personality Disorder)**

It’s defined as presence of multiple, distinct personalities that recurrently control the individual’s behavior, together with personal identity confusion. Childhood sexual abuse is a strong risk factor. Usually it occurs in a female with an occult onset, subtle clinical presentations, and delayed Dx for years.

Associated problems and differential diagnoses include chaotic interpersonal relationships, self-destructive behaviors, impulsivity, major depression, suicide attempts, sexual disorder, eating disorder, substance abuse, borderline personality disorder, PTSD, etc.

**Treatment**
Psychotherapy is used to uncover psychologically traumatic memories and to resolve the associated emotional conflicts.

**Depersonalization or Derealization Disorder**

It’s a condition of persistent or recurrent feeling of being detached from one’s mental processes or body, accompanied by intact sense of reality. It may follow a stressful event, and show jamais vu (a sense of familiar things being strange), déjà vu (a sense of unfamiliar things being familiar), and other forms of perceptual distortion.

**Treatment**

Psychotherapy is helpful in decreasing anxiety.

**Dissociative stupor**

It is a condition of a profound diminution or absence of voluntary movement and normal responsiveness to external stimuli such as light, noise, and touch, but examination and investigation reveal no evidence of a physical cause. In addition, there is positive evidence of psychogenic causation in the form of recent stressful events or problems. Diagnosis is clinical.

**Treatment**

Treatment may include removal of patient from the stressful environment, individual psychotherapy (including hypnosis), and atypical antipsychotics if necessary.

**SOMATIC SYMPTOM AND RELATED DISORDERS**

This is a group of disorders characterized by the presentation of physical symptoms without full medical explanations, and the symptoms are severe enough to interfere with the patient’s social or occupational activities.

**Primary gain:** Keeps internal conflicts outside patient’s awareness.

**Secondary gain:** Benefits received from being “sick”.

**La belle indifférence:** Patient seems unconcerned about impairment.

**Identification:** One models one’s behavior on someone who is important to him/her.

**Somatic Symptoms Disorder**

Formerly known as a somatoform disorder, it is a mental disorder characterized by multiple physical symptoms that affect multiple organs and systems without full medical explanations. They are suggestive of physical illness or injury but not attributable to another mental disorder. It more often affects low-socioeconomic, unmarried females in the 30’s.

**Diagnosis**
1. Many physical symptoms affecting multiple organs that cannot be explained fully by a general medical condition or drug effects. Most cases include more than four pain, two GI, one sexual, and one neurological symptoms.

2. Patient usually has a long, complicated medical history and impaired psychosocial functions.

   **Treatment**

   1. Therapists should have sympathy for the patient. Try to keep the same physician and make regular schedules for the patient.

   2. Individual psychotherapy is needed to help patient aware of the possible psychological nature of the symptoms and help with coping skills.

   **Conversion Disorder (Functional Neurological Symptom Disorder)**

   It’s a disorder in which the individual experiences one or more neurologic deficits after a special event that cannot be explained by any medical or neurologic diseases. It’s more common in young, low-socioeconomic and low-IQ females, and military persons. Associated disorders include passive-aggressive, dependent, antisocial, and histrionic personality disorders.

   **Diagnosis**

   Patient typically has 1-2 neurologic symptoms that affect voluntary motor or sensory functions (commonly mutism, blindness, paralysis, or paresthesia) following psychological factors. Patient is usually unconcerned about his/her impairment.

   **Treatment**

   Symptoms usually resolve spontaneously. Psychotherapy can help establish a caring relationship with the patient and help relieve stress and deal with illness.

   **Factitious Disorder**

   It’s a disorder characterized by the conscious or deliberate production of false or exaggerating symptoms and signs of both medical and mental disorders in order to assume the sick role for attention. Typically, patients have faked symptoms and signs and demand treatment in the hospital, and become angry when they are confronted or rejected, or accuse the physician or nurse if the test result is negative (indicating faked sample). It’s more frequent in male health workers. Pediatric patients may have a history of being abused and thus seek the sick role.

   If the manifestations are faked for another person (as in mother and child), it’s called “Factitious disorder by proxy”.

   **Treatment**

   There is no effective therapy. Treatment is usually alleviative management. When the physician suspects factitious disorder, be alert of the physician’s countertransference. If a “factitious disorder by proxy” is suspected, the child protective authority should be contacted for the child’s protection.
Differentiation

Malingering:

It’s a condition characterized by the conscious fabricating symptoms and signs for an obvious secondary gain (money, sick leave, etc). Individual tends to complain many subjective, exaggerated symptoms and is concerned more with rewards than with alleviation of symptoms. It’s more common in men in factories, jails, and the army. Diagnosis is generally made when there is a discrepancy between the patient’s complaints and the actual results of physical examination and lab tests. It is not considered a mental disorder. Treatment: Apply skillful doctor-patient relationship to therapies. If medical evaluation reveals malingering, then skillfully confront the patient with the results and try to save the patient’s self-respect. If confronted harshly, the patient may become angry and tougher to deal with.

Illness Anxiety Disorder (Hypochondriasis)

It refers to excessive preoccupation or worry about having a serious illness despite constant reassurance by the physician. The belief is not delusional but affects the individual’s level of functioning. Most onset ages are 20-30 years and duration > 6 months.

Treatment

Make frequent, regular schedules with the patient for psychotherapy, to help patient relieve stress and deal with illness.

Undifferentiated Somatoform Disorder (by ICD-10 and DSM-IV)

When somatoform complaints are multiple, varying and persistent, but the complete and typical clinical picture of somatization disorder is not fulfilled, it’s considered “Undifferentiated somatoform disorder”.

(Persistent Somatoform) Pain Disorder

It’s a condition of chronic pain experienced by a patient in one or more areas, and is thought to be caused by psychological stress. It’s more common in middle-aged females.

Essentials of diagnosis

1. Symptoms more than signs: Pain exists in more than one anatomic site and causes distress to the patient. Usually there is no faked pain or acts seeking secondary gain involved. Patient usually has stressful events, a long medical history, many physicians, and poor effects with standard analgesic therapies.

2. Conditions such as dyspareunia, somatic symptoms disorder, conversion disorder, or mood disorders can eliminate pain disorder as a diagnosis. Diagnosis depends on the ability of physicians to explain the symptoms and on psychological influences.

Treatment
1. Individual psychotherapy helps explore the psychological origin and emotional content of the pain.
2. TCAs, venlafaxine, biofeedback, and hypnosis may be helpful.

**Mix: Chronic Fatigue Syndrome (CFS)**

CFS is a debilitating and complex disorder characterized by **profound fatigue for longer than 6 months** that is not improved by bed rest and that may be worsened by physical or mental activity. Most patients experience partial recovery and relapses within 2 years; female > male.

**Etiology**

Unknown. It may be associated with viral infections, immunologic, neurologic, or endocrine dysfunctions.

**Essentials of diagnosis**

1. Unexplained fatigue that is not alleviated by rest, is not due to exertion, and significantly affects quality of life. Symptoms may affect several body systems and include weakness, muscle and joint pain (without redness/swelling), impaired short-term memory and/or mental concentration, insomnia, headache, sore throat, tender lymph nodes, depression, and reduced daily activities.

2. Lab tests: Usually normal and may be needed for exclusion diagnosis -- CBC, LFTs, serum electrolytes, TSH, HIV, etc. **Diagnosis of CFS is made by exclusion.**

**Differential diagnosis**

1. Psychiatric disorders: major depressive disorder (No.1 cause), anxiety disorder, somatisation, etc.
2. Endocrine disorders: hypothyroidism, poorly controlled diabetes, Addison disease, hypercalcemia (hyperparathyroidism), hypopituitarism.
4. Hematologic diseases: severe anemia, occult malignancy.
5. Cardiopulmonary diseases: CHF, obstructive sleep apnea.
7. Medications: anti-HTN medicines (clonidine, methyldopa), beta-R blockers, hypnotics, antihistamines, antidepressants (amitriptyline, doxepin, and trazodone with sedating effect), drug abuse/withdrawal.

Others: fibromyalgia, sleep disorders, etc.

**Treatment**

1. Treat known underlying cause.
2. Cognitive behavioral therapy (exercise, behavioral modifications), antidepressants, or/and NSAIDs can be helpful.
SUBSTANCE-RELATED AND ADDICTIVE DISORDERS

Substance abuse: It refers to maladaptive pattern of substance use that leads to loss of control and increased use of the substance. It includes tolerance, dependence and withdrawal, and is associated with serious medical, social, or emotional consequences. Mostly it occurs among young adults and teenagers, by millions per year in the US.

Intoxication: It’s reversible experience with a substance that leads to harmful psychological or physiological changes.

Withdrawal: It refers to cessation or reduction of a substance leading to either psychological or physiological changes.

Dependence: It refers to maladaptive pattern of substance use that leads to tolerance. There is withdrawal reaction(s) when the patient reduces doses. Patient spends most of his time obtaining and using drugs and recovering from drug use. The drug abuse is continued despite adverse consequences.

Prevalence of substance abuse by order
1. Alcohol; 2. smoking; 3. marijuana; 4. opioid; 5. cocaine; 6. others.

Etiology and risk factors
1. Family history of alcohol abuse, childhood physical or sexual abuse, poor parenting, exposure to drug use through peers or drug dealers, and social isolation.
3. Self-drug motivation: Patient may intend to use substance to alleviate some psychological symptoms (e.g., alcohol for depression).

Diagnostic guidelines
1. Maintain an extent of suspicion, be ready for denial from abusers, and try to obtain more history from close family members or friends, including familial and social function. P/E should be focused on signs of drug use (burns, needle marks, and skin infections/injury) and poor hygiene and nutrition.
2. Diagnostic lab tests:
   For alcohol abuse: serum GGT, AST (SGOT), ALT (SGPT), and LDH levels.
   For IV drug abuse: HIV, hepatitis B, hepatitis C, and TB testing.

Therapeutic guidelines
1. Preventive programs: Teach adolescents how to resist social pressures to use drugs and to enhance other social and personal skills.
2. Detoxification: Substance-specific therapies, usually taking 5-10 days in hospital to assure safety.
3. Drug rehabilitation: Stop drug abuse and develop new coping skills that make relapse less likely, usually taking 1 month or more. Self-help groups (e.g., Alcoholics Anonymous) have been the most effective treatment for many adult substance abusers, both for rehabilitation and relapse prevention.
SUBSTANCE-RELATED DISORDERS

Alcohol Use Disorder

The prevalence is 10-15% in general population. Alcohol use disorder in DSM-5 replaces alcohol abuse and alcohol dependence in DSM-IV. Alcohol use disorder can be specified as mild, moderate, or severe. Alcohol dependence in DSM-IV is best represented by moderate to severe alcohol use disorder in DSM-5; alcohol abuse is similar to the mild subtype of alcohol use disorder.

Screening test

CAGE-questionnaire—any two positive answers to the following four questions (or to the last question “d” alone) are suggestive of alcohol use disorder.

a. Have you ever felt that you should cut down your drinking?

b. Have you ever felt annoyed by others’ criticism of your drinking?

c. Have you ever felt guilty about your drinking?

d. Have you ever had a morning drink (eye-opener) to feel easier?

Diagnostic criteria

(1) Recurrent drinking resulting in failure to fulfil role obligations; (2) Recurrent drinking in hazardous situations; (3) Continued drinking despite alcohol-related social or interpersonal problems; (4) Evidence of tolerance; (5) Evidence of alcohol withdrawal or use of alcohol for relief or avoidance of withdrawal; (6) Drinking in larger amounts or over longer periods than intended; (7) Persistent desire or unsuccessful attempts to stop or reduce drinking; (8) Great amount of time spent obtaining, using, or recovering from alcohol; (9) Important activities given up or reduced because of drinking; (10) Continued drinking despite knowledge of physical or psychological problems caused by alcohol; (11) Alcohol craving.

Disorder severity — the severity of alcohol use disorder at the time of diagnosis can be specified as a subtype based on the number of symptoms present:

Mild: Two to three symptoms;

Moderate: Four to five symptoms;

Severe: Six or more symptoms.

Intoxication: Disinhibition, talkative, slurred speech, moody, ataxia, aggression, blackouts, hallucinations, impaired memory and judgment, coma. **Intoxication treatment:** B1, folate, anti-seizure (carbamazepine); avoid neuroleptics.

Withdrawal: Tremor, tachycardia, HTN, agitation, seizure, delirium tremens (DTs). **Treatment:** Long-acting BZ (chlorodiazepam, lorazepam) for sedation (especially for DTs); diazepam for prevention of seizure; beta--R blocker and clonidine for HTN, etc.

Alcohol dependence & Abuse (Alcoholism): (1) Physiologic dependence as manifested by evidence of withdrawal when intake is interrupted. (2) Tolerance to the effects of alcohol. (3) Evidence of alcohol-
associated diseases. (4) Continued drinking despite strong medical and social contraindications and life disruptions. (5) Impairment in social and occupational functioning. (6) Depression, blackouts, etc.

**Complications:** GI—gastritis, esophagitis, pancreatitis, alcoholic liver disease, Mallory-Weiss tears; CVD—alcoholic cardiomyopathy, essential HTN; CNS—Wernicke encephalopathy, Kosakoff psychosis; pulmonary—pneumonia, aspiration; sexual function—impotence, loss of libido; psychiatric—depression, anxiety, insomnia; nutritional—vitamin (B1, etc) deficiencies and GI cancers.

**Anti-abuse:** Disulfiram can induce short of breath, flushing, tachycardia, headache, nausea/vomiting shortly after alcohol intake. Naltrexone helps reduce the craving for alcohol.

**Marijuana (Cannabis)**

**Intoxication:** Euphoria, slowed sense of time, impaired judgement and motor coordination, social withdrawal, increased appetite and sexual impulse, dry mouth, conjunctival congestions, hallucinations, anxiety, paranoia. There is no obvious withdrawal or dependence.

**Treatment:** Counselling and group support. BZ is used for acute paranoid delusion.

**Cocaine**

**Intoxication:** Psychosis, agitation, euphoria, pupil dilation, tachycardia, HTN, panic, paranoia, hallucinations, violence, and sudden death.

**Treatment:** DA-R blocker (bromocriptine or haloperidol) for severe agitation; anti-HTN medicines; avoid beta-R blocker!

**Withdrawal:** Significant post-use “crash” with hypsomnolence, depression, craving, angina, nightmare and suicidality. The severe craving may strongly contribute to compulsive use.

**Amphetamines**

**Intoxication:** Psychomotor agitation, euphoria, pupil dilation, tachycardia, HTN, impaired judgment, prolonged wakefulness and attentiveness, hallucinations, and seizure.

**Treatment:** Haloperidol for severe agitation; anti-HTN medicines, etc.

**Withdrawal:** Post-use “crash” (hypsomnolence, depression, lethargy, stomach cramp, nightmare).

**Opioids**

**Intoxication:** Euphoria then apathy, CNS and respiratory suppression (lethal), pupil constriction, constipation. **Treatment:** Naloxone/naltrexone can block opioid-R and reverse effects.

**Withdrawal:** Dysphoria, insomnia, anorexia, myalgia, fever, lacrimation, diaphoresis, dilated pupils, rhinorrhea, piloerection, nausea, vomiting, stomach cramps, diarrhea, etc. **Treatment:** Short action: clonidine. Long-term: methadone or buprenorphine.
PCP (Phencyclidine)

**Intoxication:** Assaultiveness, belligerence, violence, psychosis, agitation, impulsiveness, impaired judgement, nystagmus/ataxia, tachycardia, HTN, hallucination, and delirium.

**Treatment:** Reassurance; diazepam or haloperidol for severe cases.

LSD—Hallucinogen

**Intoxication:** Marked anxiety or depression, delusion, visual hallucinations, flashbacks, pupil dilation, impaired judgement, diaphoresis, tachycardia, HTN, heightened senses.

**Treatment:** Supportive counselling; traditional antipsychotics or anxiolytics.

**Withdrawal:** Recurrence of intoxication symptoms due to GI reabsorption. Sudden onset of severe violence may occur.

Barbiturates

**Intoxication:** Low safety margin; respiratory depression.

**Withdrawal:** Anxiety, seizures, delirium, lethal CVS and respiratory inhibition. **Treatment:** Short-acting diazepams.

Benzodiazepines

**Intoxication:** Interactions with alcohol; amnesia, ataxia, somnolence, diuresis, arrhythmia, mild respiratory inhibition.

**Withdrawal:** Rebound anxiety, seizure, tremor, insomnia, and HTN. **Treatment:** Short-acting diazepam.

Caffeine

**Intoxication:** Restlessness, insomnia, diuresis, muscle twitching, arrhythmia (tachycardia), agitation.

**Withdrawal:** Headache, lethargy, depression, weight gain, irritability, craving.

Nicotine

**Intoxication:** Restlessness, insomnia, anxiety, arrhythmia.

**Withdrawal:** Irritability, headache, anxiety, weight gain, bradycardia, and distractibility.
NON-SUBSTANCE-RELATED DISORDERS

Gambling Disorder

Formerly known as “Pathological gambling in impulse control disorders”, it is a disorder characterized by persistent and recurrent gambling behavior, including a preoccupation with gambling, a need to gamble with more money, attempts to stop gambling or to win back losses, illegal acts to finance the gambling, or loss of normal relationships due to gambling. Individuals usually appear overconfident, with histories of multiple arrests, suicide attempts, alcohol abuse, loss of a loved one, poor parenting, mood disorder, etc. Prevalence is males > females.

Treatment

Gamblers Anonymous group or organization is the most effective treatment. It involves public confessions, peer pressure, and sponsors.

FEEDING AND EATING DISORDERS

Anorexia Nervosa

It’s an eating disorder characterized by failure to maintain a normal eating habit and body weight, fear and preoccupation with overweight. Patient has an unrealistic self-evaluation as overweight and disturbed body image, and usually loses weight by maintaining strict caloric control, excessive exercise, purging, fasting, and abusing laxative and diuretics. It mostly occurs in young females (F:M = 10:1). Average onset age is 17 years; the later the onset, the worse the prognosis.

Etiology and risk factors

They may be Assoc/w some genetic factors, emotional conflicts with contraception and sexuality, and a cultural emphasis on thinness.

Essentials of diagnosis (criteria)

1. Restriction of energy intake that leads to a low body weight (body mass index <18.5), given the patient’s age, sex, developmental trajectory, and physical health.
2. Intense fear of gaining weight or becoming fat, or persistent behavior that prevents weight gain, despite being underweight.
3. Distorted perception of body weight and shape, undue influence of weight and shape on self-worth, or denial of the medical seriousness of one’s low body weight.

Patient typically restricts food intake and maintains diets of low-calorie foods to lose weight; it may be accompanied with exercise and purging (self-induced vomiting or laxation); over-concerns with appearance and overweight; has amenorrhea ≥ 3 cycles; denies emaciated conditions; may have OCD or depression. Symptoms are usually > 3 months.

There are two subtypes:
(1) **Restricting type** -- Marked by weight loss through dieting, fasting, and excessive exercise without recurrent episodes of binge eating or purging.

(2) **Binge eating and purging** -- Marked by episodes of binge eating and purging.

**P/E results:** **Body weight is \( \geq 15\% \) below expected weight:** emaciation, hypotension, bradycardia, lanugos (fine hair on the trunk), and peripheral edema. Signs of purging: eroded dental enamel and scarred/scratched hands. **Lab** tests may show electrolyte disturbances (Hypo-KCl alkalosis, metabolic acidosis, etc).

**Treatment**

1. First hospitalize the patient and correct metabolic imbalance to prevent dehydration, starvation, electronic imbalances, and death.

2. Weight gain is the target. It's important to have psychotherapy and behavior therapy (with rewards or punishments) based on weight, and family therapy to reduce conflicts with parents. Antidepressants (SSRIs) may have some effects on promoting weight gain. Patient is usually not distressed by the disorder and may be **resistant to treatment**.

3. Prognosis/outcome: The course is fluctuating; long-term mortality rate of hospitalized patients is 10%, resulting from the effects of starvation (electrolyte disorders) and purging or suicide.

**Bulimia Nervosa**

It's an eating disorder characterized by frequent **binge-eating and purging and normal body weight, with the self-image unduly influenced by shape and weight and lack of control of overeating episodes.** It mostly occurs among **young females.** It may be in chronic or intermittent course with high remittances.

**Risk factors**

Psychological conflicts (guilt, helplessness, etc.) and mood disorders. Worse prognosis is predicted if substance abuse is co-existent.

**Essentials of diagnosis**

1. The most common symptoms are lethargy, irregular menses, abdominal pain and bloating, and constipation. Typical behaviors include recurrent episodes of binge-eating associated with emotional stress and followed by feelings of guilt, self-recrimination, and inappropriate compensatory behaviors of self-induced vomiting or laxation, fasting, or excessive exercise to avoid weight gains.

2. Attempts to conceal binge-eating or purging, or lies about the behavior. It may be accompanied by symptoms of depression, substance abuse, or personality disorder.

3. **P/E results:** Evidence of purging and/or laxative/diuretic abuse (on hands, teeth, etc).

**Differential diagnosis**

Binge-eating disorder; anorexia nervosa; atypical depression; borderline personality disorder.

**Treatment**
Cognitive and behavioral therapy is the major treatment. It’s more effective if combined with psychodynamic psychotherapy and antidepressants (SSRIs). Patient is usually distressed by the disorder, willing to be treated, and thus easier to treat.

**Binge-Eating Disorder (BED)**

BED is an eating disorder characterized by binge eating without subsequent purging episodes.

**Essentials of diagnosis**

1. Each binge consists of eating an amount of food much larger than most people would eat in a similar period of time under similar circumstances, and is accompanied by a feeling of discomfort, nausea/vomiting, and loss of control. **It occurs at least once a week for 3 months.**
2. The binge eating is not associated with the recurrent use of appropriate compensatory behavior and does not occur exclusively during the course Bulimia Nervosa or Anorexia Nervosa.
3. The person is seriously worried about the binge eating, feeling disgusted, depressed, or guilty after binge eating. These conditions may be associated with obesity, which is present with 2/3 of people with BED, although most people with obesity don’t have BED.

**Treatment**

Strategies are similar to those for bulimia nervosa. Effects are usually good because patient is willing to be treated.

**Pica (Disorder)**

Pica is characterized by an appetite for substances largely non-nutritive, such as ice, clay, chalk, dirt, or sand. To be diagnosed as a disorder, it must persist for more than 1 month at an age where eating such objects is considered developmentally inappropriate, not part of culturally sanctioned practice and sufficiently severe to warrant clinical attention. The consumption of ice is common and harmful as there is a high risk of tooth cracking, enamel deterioration, jaw joint strain, and GI lesion. Anemia and lead and zinc poisoning are common complications. Pica is more commonly seen in women and children.

**Treatment**

It may vary by patient and suspected cause (e.g., child, disabled, pregnant or psychotic) and may emphasize psychosocial, environmental, and family-guidance approaches. Iron deficiency may be treatable though iron supplement.

**Rumination Disorder (Syndrome)**

Also called Merycism, it is an under-diagnosed chronic motility disorder characterized by effortless regurgitation of most meals following consumption, due to the involuntary contraction of the muscles around the abdomen. There is no retching, nausea, heartburn, odor, or abdominal pain associated with the regurgitation, as there is with typical vomiting. Other findings include acid-induced erosion of the esophagus and enamel, halitosis, malnutrition, severe weight loss, and an unquenchable appetite. Cycles of ingestion and regurgitation can mimic the binging and purging of bulimia.

**Treatment**
There is no known effective therapy for rumination. Treatment is different for different ages and conditions. Biofeedback and relaxation techniques may be tried for adults.

**Avoidant/Restrictive Food Intake Disorder (ARFID)**

Also known as Selective Eating Disorder (SED), it is an eating disorder that prevents the consumption of certain foods. It is often viewed as a phase of childhood that is generally overcome with age. Some people may continue to be afflicted with ARFID throughout their adult lives.

**Diagnostic criteria** include: (1) Disturbance in eating or feeding certain foods; (2) Substantial weight loss or absence of expected weight gain; (3) Nutritional deficiency; (4) Dependence on a feeding tube or dietary supplements; (5) Significant psychosocial interference; (6) Excluding other disorders.

**Treatment**

Most children can benefit from a 4-stage “4R” treatment program at home based on systematic desensitization -- Record, Reward, Relax, and Review. Most adults’ symptoms eventually disappear without treatment.

**SLEEP-WAKE DISORDERS**

**Normal Sleep**

**Two major stages**

1. **Nonrapid eye movement sleep (NREM):** Characterized by slowing of the EEG rhythms, high muscle tone, and absence of eye movements and thought activity. In this stage the brain is inactive while the body is active. It consists of 4 sub-stages:

   Stage-1: EEG shows alpha and theta waves. Stage-2 (45%, longest): Kappa (k)-complex and sleep spindles. Stage-3: Delta-waves (slowest, “slow wave sleep”). Stage-4: Continuation of delta-waves.

2. **Rapid eye movement sleep (REM):** 25%, with aroused EEG patterns (sawtooth waves), sexual arousal, rapid eye movements, generalized muscle atony, and dreams (nightmares). In this stage, the brain is active and the body is inactive.

**Changes in sleep patterns from infancy to old age**

Total sleep time and REM% decrease. Stages 3 and 4 tend to vanish.

**Changes in neurotransmitters during sleep**

There are increased 5-HT and ACh, and decreased NE (noradrenaline) and DA (dopamine).

**Sleep Disorders**

The International Classification of Sleep Disorders (ICSD-3) and DSM-5 have the following similar categories of sleep disorders:

**Insomnia (Disorder)**

It’s a disorder characterized by difficulties in initiating or maintaining sleep followed by frequent yawning and tiredness during the day, not due to physical or mental causes. It commonly affects up to 30% of the population at the level of functioning and is exacerbated by anxiety. It must be present > 3 times/week for 1 month for diagnosis. Acute or transient insomnia is usually due to psychological stress or travel over time zones. Chronic causes can be various from psychiatric, medical, medicinal, and primary.

**Treatment**

1. **Good sleep hygiene techniques:** Establish regular sleep schedule; avoid daytime naps, evening stimulation (including CNS stimulants, alcohol). Treat underlying cause if possible.
2. If it fails, try benzodiazepines (short-term -- triazolam; intermediate -- estazolam, lorazepam, temazepam; long-acting -- flurazepam, quazepam), non-BZ (zolpidem), melatonin agonist (ramelteon), or diphenhydramine shortly (< 2-3 weeks).

**Breath-related Sleep Disorders (Sleep-related Breathing Disorders)**

They are characterized by abnormal respiration during sleep, occurring in both adults and children. There are four major types: (1) Central sleep apnea syndrome; (2) Obstructive sleep apnea (hypopnea) syndrome; (3) Sleep related hypoventilation disorder; (4) Sleep related hypoxemia disorder.

They can be further divided according to their etiology.

**Sleep apnea syndrome** is a disorder with cessation of airflow at the nose or mouth during sleep. These apneic episodes usually last > 10-20 sec/each, characterized by a loud snore followed by a heavy pause. It’s considered pathologic if > 5 episodes/hr or > 30 episodes per night. It may be associated with depression and daytime sleepiness. Risk factors include obesity, family history, alcohol or sedative intake, hypothyroidism, and structural abnormalities.

**Clinical features, subtypes, and diagnosis**

1. Mostly seen in **obese, middle-aged males**. Patient usually presents with snoring and apnea at night, and dry mouth, fatigue, headache and sleep during the day. Spouse complains of being interfered during the night. Patient may develop arrhythmias, hypoxemia, pulmonary HTN, and sudden death (especially infant and elderly).
2. **Central sleep apnea (CSA):** There is no central respiratory effort during the pause in breathing. After the episode of apnea, breathing may be faster (hyperpnea) for a period of time as a respiratory compensation. CSA can be primary (idiopathic) or secondary (#1 associated with Cheyne-Stokes breathing).
3. **Obstructive sleep apnea/hypopnea (OSA):** OSA is characterized by repetitive, intermittent episodes of airflow reduction (hypopnea) or cessation (apnea) due to upper airway collapse during sleep, including adult type and pediatric type. The airway collapse is due to muscle atonia in oropharynx or nasal, tongue, or tonsil obstruction. Each apneic period usually lasts 20 to 30 seconds and results in hypoxia, which arouses the patient from sleep. This occurs multiple times overnight.

4. **Diagnosis:** Sleep test (polysomnography) is the most accurate means of diagnosis. It can record decreased O\textsubscript{2} saturation and distinguish OSA from CSA, seizures, etc.

**Treatment**

1. **CSA:** Try to target underlying cause. (1) Continuous positive airway pressure (CPAP) is usually tried first (especially with Cheyne-Stokes breathing). (2) If failed, adaptive servo-ventilation (ASV) is tried. (3) If both CPAP and ASV are failed, bi-level positive airway pressure (BPAP) is tried with a backup respiratory rate. (4) If these cannot be tolerated, medications (acetazolamide, zolpidem, or triazolam) can be tried (if no risk factors for respiratory depression).

2. **OSA:** (1) Mild to moderate cases: patient education and behavior therapy-- weight reduction (for obese people), avoidance of alcohol/sedatives intake and supine position during sleep.

   (2) Severe OSAHS (>20 apneic episodes with arterial oxygen desaturations)-- continuous (fixed) positive airway pressure (CPAP) is the main therapy, which can prevent occlusion of the upper pharynx. If not tolerated, BPAP is an option. If this fails, uvulopalatopharyngoplasty (to remove redundant tissue in oropharynx) or an upper airway stimulation system may be tried.

   (3) Children-- surgery for tonsillar/adenoidal hypertrophy.

**Central Disorders of Hypersomnolence and Hypersomnolence Disorder**

These disorders refer to excessive daytime sleepiness that is not due to disturbed sleep or misaligned circadian rhythms. In ICSD-3, central disorders of hypersomnolence include narcolepsy type 1 and type 2, idiopathic hypersomnia, and Kleine-Levin syndrome (KLS, recurrent hypersomnia). KLS is a rare disorder that starts during adolescence and has a male gender preference. The patients have recurrent episodes of hypersomnia, which are often associated with compulsive overeating and hypersexuality.

**Hypersomnolence Disorder**

It is characterised by excessive daytime sleepiness that is not due to medical or mental conditions, drugs, poor sleep hygiene, insufficient sleep, or narcolepsy. It occurs at least three times per week for at least 3 months and causes significant distress or impairment in social or occupational functioning. This disorder is less well-defined and lack of REM sleep and other features of narcolepsy.

**Treatment**

**Psychostimulants** (methylphenidate or amphetamine) is the choice of treatment. SSRIs may be helpful in some patients.
Narcolepsy

Also known as hypnolepsy, it is a chronic neurological disorder involving the loss of the brain’s ability to regulate sleep-wake cycles normally, characterized by excessive daytime sleepiness and abnormalities of REM sleep for more than 3 months, causing significant impairment in social or occupational functioning. It’s an inherited disorder of variable penetrance. REM sleep usually occurs in less than 5 min. Patients feel refreshed upon awakening.

Clinical features and diagnosis

1. Involuntary “sleep attacks”: Most common symptoms—frequent irresistible sleeping at any time of day (during any activity) that lasts several min, refreshed upon awakening, and falling asleep quickly at night.

2. Cataplexy (70%) -- pathognomonic sign: Sudden loss of muscle tone, which may have been precipitated by a loud noise or intense emotion.

3. Hypnagogic and hypnopompic hallucinations: Dreaming while awaking; it occurs as the patient is going to sleep and is waking up from sleep, respectively.

4. Sleep paralysis: Patient cannot move when waking up.

Treatment

1. Forced naps at a regular time of day is usually helpful.

2. A psychostimulant (methylphenidate or amphetamine) is the main medical treatment. TCAs can be used if cataplexy is present.

Parasomnias

Parasomnias are undesirable physical events (movements, behaviors) or experiences (emotions, perceptions, dreams) that occur during entry into sleep, within sleep, or during arousals from sleep. The behaviors can be complex and appear purposeful; however, the patient is not consciously aware of the behavior. The sub-category includes:

(1) NREM related parasomnias: they are disorders of arousal including confusional arousals, sleepwalking, sleep terrors, and sleep related eating disorder

(2) REM related parasomnias: involve the intrusion of the features of REM sleep into wakefulness (eg, sleep paralysis), exaggeration of the features of REM sleep (eg, nightmare disorder), etc.

(3) Other parasomnias without specific relationship to sleep stage: exploding head syndrome, sleep related hallucinations, sleep enuresis, and drug-associated parasomnias.

Nightmare (disorder): It occurs commonly in 50% of the population. Patient can remember the event upon awakening. It increases during times of stress. There is no special therapy required but adjustment of stress.

Night terror: Awakened by scream or intense anxiety. Patient usually has no memory of the event the following day. It’s more common in boys and with family history. No special treatment is needed. If severe, limited use of BZs may be considered.
Sleepwalking: It occurs during stage 3-4 of sleep, with sequencing behaviors during sleep without full consciousness; ends in waking embarrassment without remembering anything. It’s more common in young boys and may be associated with neurologic diseases. **Treatment:** First assure patient’s safety. If it occurs frequently, give BZs to suppress stage 3-4 sleep.

**Sleep-related Movement Disorders**

These are characterized by simple, stereotypic movements that disturb sleep and cause related symptoms (daytime sleepiness, fatigue, etc). Patients may or may not be aware of the movements.

The classic disorders include restless legs syndrome, periodic limb movement disorder, sleep related leg cramps, sleep related bruxism (teeth grinding), and sleep related rhythmic movement disorder.

**Circadian Rhythm Sleep-Wake Disorder**

It’s characterized by chronic or recurrent sleep disturbance due to misalignment between the environment and an individual’s sleep-wake cycle. People with the disorder are unable to sleep and wake at the times required for normal work, school, and social needs. They are generally able to get enough sleep if allowed to sleep and wake at the times dictated by their body clocks. The quality of their sleep is usually normal. There are several types of circadian rhythm disorders:

1. **Shift work disorder and jet lag disorder** are the most common types, although most of these cases do not come to medical attention.
2. **Delayed sleep-wake phase disorder** is characterized by sleep and wake times that are habitually delayed compared to conventional times, more common in a younger patient.
3. **Advanced sleep-wake phase disorder** is characterized by sleep and wake times that are habitually early compared to conventional time, more common in the elderly.
4. **Irregular sleep-wake rhythm disorder** is characterized by lack of a clearly defined circadian rhythm of sleep and wake. This disorder is commonly associated with developmental disorders in children and with neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and Huntington disease.

**Treatment**

2. Shift-work disorder: Light therapy may help.
3. Delayed sleep-phase disorder: Taking oral melatonin 30 min before bedtime may help.

**SEXUAL DISORDERS**

**Terminology of Human Sexuality**

Sexual identity: Based on a person’s secondary sexual characteristics.

Gender identity: Based on a person’s sense of maleness or femaleness, mostly established by age 3.
Gender role: Based on a person’s external patterns of behavior that reflect the inner sense of gender identity.

Sexual orientation: Based on a person’s choice of love object, which can be heterosexual (most population), homosexual, bisexual, or asexual.

**Sexual Function Changes with Aging**

Interest in sexual activity usually does not decrease with aging, but sexual functions do.

**Male:** It requires longer time for the genital stimulation and reaching orgasm, and has longer refractory period before next orgasm. Intensity of orgasm is mostly decreased.

**Female:** Menopause and decreased estrogen cause vaginal dryness and discomfort during coitus, which can be treated with hormone replacement therapy (HRT) or vaginal creams (estrogen). Increased orgasm after 30-35 y/a is common.

**SEXUAL DYSFUNCTIONS**

Sexual dysfunction disorders refer to disturbances in sexual arousal, desire, orgasm, or pain with sexual intercourse. They may be classified into the related four categories—sexual desire disorders, arousal disorders, orgasm disorders, and sexual pain disorders. Sexual dysfunction requires a person to feel extreme distress and interpersonal strain for a minimum of 6 months (excluding substance or medication-induced sexual dysfunction).

Sexual dysfunctions can have a profound impact on an individual’s perceived quality of sexual life. The prevalence is up to 30-40% and it occurs at least once in a lifetime. **2/3 of all cases are due to biomedical factors.** 1/3 of cases are due to psychological conditions (known as “psychosexual disorders”).

**I. Sexual Desire Disorders**

Also known as hypoactive sexual desire disorder or decreased libido, it is characterised by a lack or absence of sexual desire for sexual activity or of sexual fantasies for certain period of time. The condition may have started after a period of normal sexual functioning or the person may always have had no/low sexual desire. It’s **more common in women** with heavy burdens of dual duty of work and home care.

General causes may include aging, stress, fatigue, pregnancy, medications (such as antidepressives, antihypertensives, antipsychotics, antiparkinson drugs, and lithium), psychiatric conditions (such as depression, anxiety disorders, and panic disorder), or decrease in normal estrogen in women or testosterone in both men and women.

**Treatment**

II. Sexual Arousal Disorders

Previously known as frigidity in women and impotence in men, they are now corrected as sexual arousal disorders (including erectile dysfunction). These conditions can manifest themselves as an aversion to, and avoidance of, sexual contact with a partner. In men, there may be partial or complete failure to attain or maintain an erection, or a lack of sexual excitement and pleasure in sexual activity.

Causes may include medications (such as antidepressives, antihypertensives, antipsychotics, antiparkinson drugs, and lithium), chronic diseases (such as diabetes and cardiovascular disease causing decreased blood flow to the genitalia), surgical or traumatic injury to the nervi erigentes, etc), and psychological conditions (including relationship between the partners).

Erectile dysfunction (ED), also known as impotence, it is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis. The causes may be psychological or physical (as stated above). It is estimated that up to 50% of all men between the ages of 40 and 70 have some form of ED; 80% of cases are organic.

Treatment

It includes psychological and medical therapies according to underlying cause. Sildenafil as a vasodilator is the effective remedy for ED. Be aware of its adverse effect or risk for cardiac ischemia.

Premature ejaculation

It refers to the condition when ejaculation occurs before the partner achieves orgasm or a mutually satisfactory length of time has passed during intercourse. Generally, premature ejaculation is thought to occur when ejaculation occurs in less than 2 minutes from the time of the insertion of the penis. It is the most common presentation of male sexual dysfunctions (30-40% of cases).

Causes: Although historically attributed to psychological causes (#1 is anxiety), new studies suggest an underlying neurobiological cause may also lead to premature ejaculation.

Diagnosis: The patient must have a chronic history of premature ejaculation, poor ejaculatory control, and the problem must cause feelings of dissatisfaction as well as distress the patient, the partner or both.

Treatment: Psychotherapy and behavioral modification techniques (pause and penile squeeze, etc).

III. Orgasm Disorders

These refer to persistent delays or absence of orgasm following a normal sexual excitement phase. The disorder can have physical, psychological, or pharmacological origins, and more common in females.

Causes: Medications (such as antidepressives, antihypertensives, antipsychotics, antiparkinson drugs, and lithium) are a common medical cause, as they can delay orgasm or eliminate it entirely. Other causes may include chronic diseases (CVD, endocrine-metabolic), mental disorders, and substance abuse, etc.

Treatment

Treat underlying conditions, change medications, and give cognitive behavioral therapy, etc.
IV. Sexual Pain Disorders

The disorders are also known as dyspareunia (painful intercourse) or vaginismus (an involuntary spasm of the muscles of the vaginal wall that interferes with intercourse) and affect women almost exclusively.

**Causes:** Fear and anxiety about sex; insufficient vaginal lubrication (due to insufficient excitement and stimulation, or due to hormonal changes caused by menopause, pregnancy, breast-feeding, or contraceptive creams and foams); genital inflammation; past sexual trauma (such as rape or abuse), etc.

**Treatment**

Treat underlying condition. Vaginismus is treated with psychotherapy and dilator therapy.

**Further diagnostic guidelines for sexual dysfunctions**

1. **No.1** factor of diagnostic evaluation is detailed history.
2. **P/E:** A digital rectal examination (DRE) and neurologic examination should be done. Assess for signs of peripheral vascular disease.
3. **Lab tests:** CBC, chemistry panel, fasting glucose, and lipid profiles. If hypogonadism is suspected, serum testosterone, prolactin and thyroid profile should be tested.
4. **Nocturnal penile tumescence:** If normal erection occurs during sleep, a psychogenic cause is suspected; if it does not occur, an organic cause is likely.
5. Psychological testing may be appropriate in some cases.

**Further therapeutic guidelines for sexual dysfunctions**

Specific treatment is determined by the specific cause.

1. For most organic causes, address atherosclerotic risk factors.
2. If it’s a case of abrupt sexual dysfunctioning, psychotherapy is effective.
3. If it’s traumatic erectile dysfunction, pudendal artery revasculation may be needed.
4. For hypogonadism, hormone replacement is the therapy.
5. Sildenafil (Viagra) can dilate arterioles and promote penile smooth muscle relaxation and erection. It may be helpful in patients with atherosclerotic etiologies. Contraindications include heart diseases, simultaneous use with nitrates, etc.

**GENDER DYSPHORIA**

Previously known as “Gender Identity Disorder”, it is a condition in which the individual has strong, persistent cross-gender identity and discomfort (dysphoria) with one’s biological sex or gender role without intersexual disorders. Patient usually has a history of dressing like the opposite sex, using toys assigned to the opposite sex, playing with opposite-sex children at a young age, taking sex hormones,
or/and seeking surgeries to change the gender. It’s more common in males, and may be Assoc/w depression, anxiety disorder, substance abuse, and personality disorder.

Transsexualism refers to the people with gender dysphoria having a strong and persistent desire to live according to their gender identity (opposite sex), rather than their biological (anatomic) sex.

Transvestism refers to a person occasionally wearing clothes typically associated with the opposite gender (cross-dressing) for a variety of reasons.

Treatment
First give patient education and counselling about culturally acceptable values and patterns, and then supply supportive psychotherapy.

PARAPHILIC DISORDERS

These are also classified as Sexual Arousal Disorders, Disorders of Sexual Preference, or Disorders of Adult Personality and Behavior.

Paraphilies refers to powerful and persistent sexual interest and arousal to objects, situations, or individuals that are not part of normative stimulation and that may cause serious social distress or consequences for the paraphiliac or associated individuals. A paraphilia involves sexual arousal and gratification towards extreme sexual behavior, mostly seen in men.

Specific types

Pedophilic disorder: Sexual preference for children (boys or girls or both) and recurrent urges involving sexual activities with prepubertal or early prepubertal children.

Exhibitionistic disorder: Recurrent urges or sexual arousal from exposing the genitalia to strangers (usually of the opposite sex), without inviting closer contact. This is usually followed by sexual excitement and masturbation.

Voyeuristic disorder: Recurrent urges or sexual arousal from observing unsuspecting person’s unclothed or sexual activities. This usually leads to sexual excitement and masturbation.

Frotteuristic disorder: Sexual arousal from rubbing one’s genitalia against a nonconsenting person in crowded public places.

Fetishistic disorder: Recurrent urges or sexual arousal from nonliving objects or nongenital body parts (leather, silk, underwears, feet, etc).

Transvestic disorder: Recurrent urges of cross-dressing for sexual arousal.

Sexual sadism disorder: Recurrent urges or sexual arousal from inflicting suffering (pain, bondage, or/and humiliation) on sexual partner.

Sexual masochism disorder: Recurrent urges or sexual arousal from being hurt, humiliated, bound, or abused by sexual partner.
Sadomasochism: A preference for sexual activity that involves the infliction of pain or humiliation, or bondage. If the subject prefers to be the recipient of such stimulation this is called masochism; if the provider, sadism. Often an individual obtains sexual excitement from both sadistic and masochistic activities.

Multiple disorders of sexual preference: Sometimes more than one abnormal sexual preference occurs in one person and there is none of first rank. The most common combination is fetishism, transvestism, and sadomasochism.

Therapeutic guidelines for paraphilic disorders
1. Individual psychotherapy.
2. Behavioral modifications: aversive conditioning may help.
3. Antiandrogens or SSRIs can reduce sexual drive.

NEUROCOGNITIVE DISORDERS
See Chapter 10: Diseases of the Nervous System and Special Senses, page 357.

MIX: SUICIDALITY AND DEATH

Suicidality
Suicide is the act of a human being intentionally causing his or her own death. Major risk factors include psychiatric disorders, hopelessness, and prior suicide attempts or threats.

Over one million people commit suicide every year. The World Health Organization estimates that it is the 13th-leading cause of death worldwide. It’s rated the 6-8th cause of death in the US. It is a leading cause of death among teenagers and adults under 35, and rates are higher in males than females. There are an estimated 10 to 20 million non-fatal attempted suicides every year worldwide.

Views on suicide have been influenced by varieties of cultures, values, religions, and beliefs.

Risk factors
Men, older adults, social isolation, financial or interpersonal distress, psychiatric or organic disorders --depression, bipolar disorder, schizophrenia, alcoholism, substance abuse, late-stage disease (such as cancer), other adverse situations, and previous attempts. High impulsivity and alcohol/substance abuse increases the risk that suicidal impulses will be carried out.

Presentation
Recent suicide attempt; complaints of suicide thought; admission of suicide thought; evidence of suicide behavior—collecting sleeping pills, writing a will, giving away possessions, buying weapons, etc.

Management
1. Guidelines: hospitalize patient at risk; prevent with serious safety procedures; treat with support, necessary medicine, and psychotherapy.
2. Recommendations: (1) Patients suspected to be at risk for suicide should be evaluated for suicidal ideation, intent, and prevention. (2) Patients at imminent risk for suicide require immediate psychiatric care and continuous monitoring. (3) After patient’s safety is ensured, underlying factors of psychiatric disorders, precipitating events, and on-going life circumstances should be addressed with medications, counselling, and involvement of friends, family, and religious/community groups as appropriate. (4) For patients with mood disorders who remain at risk for suicide following proper cares, lithium maintenance +/- other medications and/or psychotherapy is recommended. (5) Patients are at increased risk for suicide soon after discharge from psychiatric inpatient care. After a suicide attempt, psychotherapy may prevent subsequent attempts, and patient should be monitored closely with follow-ups. Please note that after a suicide, friends, family, and coworkers may be at increased risk for suicide and for posttraumatic stress disorder and depression.

Death and Dying

Based on the dying stages defined by Elisabeth Kubler-Ross, dying patients do not follow a simple, regular series of responses; most patients experience the following common stages of death reactions (may not be in this order).

Stage 1. Shock and denial: “No, impossible!”
Stage 2. Anger: “Why me?”
Stage 3. Bargaining: “If you…… then I will……”
Stage 4. Depression: Silent and down.
Stage 5. Acceptance: Cooperative.
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HIGH-YIELD CLINICAL IMAGES

(Courtesy images reorganized from www.images.google.com and related websites for public sharing)

Image 1-2. Normal heart anatomy and EKG (ECG): SA and AV nodes are supplied mostly by the right coronary artery (RCA), which supplies the inferior portion of the L-Ventr (via the posterior descending artery). Most coronary artery occlusions occur in the LAD (L-anterior descending artery), which supplies the anterior inter-ventr septum.

3a
3b
3a. Atrioventricular (AV) block: 1$^\circ$: P-R interval $>0.02$s; 2$^\circ$: P wave occurs without QRS; 3$^\circ$: No P before QRS, escape rhythm.
3b. Premature Ventr-contraction: early, wide QRS complex without a preceding P followed by a compensatory pause.

4. Hypo-K and hyper-K: flat T wave vs peak T wave. QRS complex can be irregular with severe hyper-K.
5. Atrial fibrillation: wavy baseline without discernible P waves; variable QRS response
6. Atrial flutter: regular rhythm; “sawtooth” P waves; varying A-V conduction (5:1 and 4:1)

7. Ventricular tachycardia: ≥ 3 consecutive PVCs; regular, rapid wide-complex rhythms
8. Ventricular fibrillation: totally erratic tracing, requiring emergent defibrillation to save life

9. Anterior wall MI: ST-elevation in leads V1-V5 with reciprocal ST-T in the inferior leads (aVR, aVL)
10. Inferior wall MI: ST-elevation in leads II, III, and aVF with reciprocal ST-T in the anterior leads (V1-V3)

11. Chronic bronchitis: thickening of bronchial walls and increased linear markings + enlarged cardiac shadow
12. Lobar pneumonia: lobar consolidation and air bronchograms
13. Asthma, emphysema, and bronchiectasis: hyperinflated lungs and flattened diaphragm indicating asthma and emphysema; streaky shadowing and bronchial wall thickening in both lungs indicating bronchiectasis

14. Cardiogenic pulmonary edema (CHF): increased vascular shadows in all lobes + enlarged left atrium

15. Pneumoconiosis: multiple small irregular opacities and interstitial densities

16. Sarcoidosis: bilateral hilar adenopathy

17. Small-cell lung cancer with lymphadenopathy: CT confirms enlarged left hilum and mediastinum

18. Orbital cellulitis: proptosis, painful eyes, decreased eye movement, and red swollen eyelids

19. Chalazion: meibomian gland lipogranuloma

20. Hordeolum (Stye): “Horrible Staph”—eyelid infection

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