LEARNING OBJECTIVES

List the signs and symptoms of septicemia
Differentiate gram-negative sepsis, gram-positive sepsis, and puerperal sepsis.
Describe bacterial endocarditis and rheumatic fever.
Discuss the epidemiology of tularemia, brucellosis, anthrax, gas gangrene.
Describe pathogens that are transmitted by animal bites and scratches.
Compare and contrast the causative agents, vectors, reservoirs, symptoms, treatments, and preventive measures for plague, Lyme disease, and Rocky Mountain Spotted Fever.
Describe infectious mononucleosis.
Compare and contrast the causative agents, vectors, reservoirs, and symptoms for yellow fever,
Compare and contrast the causative agents, modes of transmission, reservoirs, and symptoms for Ebola hemorrhagic fever and Hantavirus pulmonary syndrome.
Compare and contrast the causative agents, modes of transmission, reservoirs, symptoms, and treatments for Chagas’ disease, toxoplasmosis, malaria, and babesiosis.
Describe Swimmer’s Itch
Sepsis and Septic Shock

**Sepsis**: SIRS caused by spread of bacteria or their toxin from a focus of infection.

**Septicemia**: Sepsis involving proliferation of pathogens in the blood.

**Gram-negative sepsis** can lead to **septic shock**.

Antibiotic-resistant enterococci and group B streptococci cause **gram-positive sepsis**.

**Puerperal sepsis** (*S. pyogenes*): due to uterus infection following childbirth or abortion; can progress to peritonitis or septicemia.
Bacterial Infections of the Cardiovascular and Lymphatic Systems

- Subacute Bacterial Endocarditis
- Rheumatic Fever
- Tularemia
- Brucellosis
- Anthrax
- Gas Gangrene
- Bite Wounds
Subacute Bacterial Endocarditis:

- usually caused by alpha-hemolytic streptococci from mouth (dentist!)
- Preexisting heart abnormalities are predisposing factors.
- Signs include fever, anemia, and heart murmur.

Acute bacterial endocarditis: usually caused by *S. aureus* → rapid destruction of heart valves.

Pericarditis: Streptococci
Endocarditis

Fibrin-platelet vegetations

Normal appearance

Fig 23.4
Rheumatic Fever

Autoimmune complication of *S. pyogenes* infections. Expressed as arthritis or heart inflammation. Can result in permanent heart damage.

Antibodies against group A $\beta$-hemolytic streptococci react with streptococcal antigens deposited in joints or heart valves or cross-react with heart tissue.

Rheumatic fever can follow **strep throat**. Bacteria might not be present at time of rheumatic fever.

Prompt treatment of streptococcal infections can reduce the incidence of rheumatic fever.
“Rabbit fever” caused by *Francisella tularensis*

Bacteria reproduce in phagocytes

Transmitted by bites and scratches of infected animals, carcass handling, tick bites (~ 200 cases/year)

Ulcer at the site of entry and enlargement of the regional lymph nodes → Ulcero-glandular form (most common, plaguelike)

Aerosol infection → pneumonic form (bio weapon!)
Ulceroglandular Tularemia

Girl with ulcerating lymphadenitis colli due to tularemia, Kosovo, April 2000.
FIGURE 2. Reported cases* of tularemia — United States, 1990–2000

Number of Cases†

- 1
- 18
- 39

MV in MA
Brucellosis (Undulant Fever)

- **B. abortus** (cattle, elk, bison), **B. suis** (swine), **B. melitensis** (goats, sheep, camels)
- *Brucella*, gram-negative rods, grow in phagocytes
- Undulating fever spikes to 40°C each evening
- The bacteria enter through minute breaks in the mucosa or skin, reproduce in macrophages, and spread via lymphatics to liver, spleen, or bone marrow.
- Contact with infected animals (slaughterhouse workers, veterinarians, farmers, dairy workers) – also via ingestion of milk or milk products. 100-200 cases/y; worldwide incidence ~ 500,000.
- Mortality rate ~ 2 % (endocarditis)
Well-formed hepatic granuloma from a patient with brucellosis.
Methylene blue stain: Cultured human macrophage infected with *Brucella melitensis*. Coccobacillary bacteria replicate in phagolysosomes (original magnification x 1,000). Photograph: Courtesy of Robert Crawford, Ph.D., Senior Scientist, American Registry of Pathology, Washington, DC.
Anthrax

*Bacillus anthracis* G+ rod, ES, aerobic, virulence factors: capsule, 3 exotoxins

Zoonosis; found in soil

Cattle routinely vaccinated

In human

- **Pulmonary anthrax** (woolsorter”s disease), Inhalation of endospores; 100% mortality
- **Cutaneous anthrax**, most common, endospores enter through minor cut; 20% mortality
- **Gastrointestinal anthrax**: Ingestion of undercooked contaminated food; 50% mortality

Treated with ciprofloxacin or doxycycline
Bacillus anthracis infects mostly farm animals and is usually spread to humans through a break in the skin.
Gas Gangrene (Clostridial Myonecrosis)

**Gangrene:** Soft tissue death from ischemia $\Rightarrow$ especially susceptible to growth of anaerobic bacteria such as:

**C. perfringens,** G+ rod, ES, anaerobic, release of $\alpha$ toxin (cytotoxic), H$_2$ and CO$_2$

Ubiquitous in soil and dust – “war disease”

*C. perfringens* can invade the wall of the uterus during improperly performed abortions

Death due to toxemia

Treatment: debridement and amputation – hyperbaric chamber; antibiotics and antitoxin of limited value (why?)
generally occurs at wound or surgical site → painful swelling and tissue destruction. Rapidly progressive, often fatal.
Animal Bites and Scratches

Anaerobic bacteria infect deep animal bites

*Pasteurella multocida* – normal flora of oral and nasopharyngeal cavity of dogs and cats; may cause septicemia

*Bartonella henselae* – (rickettsia) **Cat scratch disease**. Relatively common (~20,000 cases in US) – mostly in young – occasionally serious

**Human bites** – (not in book) normal mouth flora (incl. *S. aureus*, α hemolytic *S. viridans*, *H. influenza* and various anaerobes)
This gentleman presented with a draining sinus on the dorsal aspect of his proximal phalanx, about one month after sustaining a clenched fist bite injury. He could not clearly recall details of his initial treatment.
leading to Osteomyelitis

Evidence of osteomyelitis with bone erosion and subperiosteal bone formation (arrows).
Vector-Transmitted Diseases

- Plague
- Relapsing Fever
- Lyme Disease
- Ehrlichiosis
- Typhus
- Epidemic Typhus
- Spotted Fevers
"Black death": *Yersinia pestis*, G- rod, bipolar staining

Endemic in Southwest → sylvatic plague

Reservoir: Rats, ground squirrels, and prairie dogs

Vector: infected fleas

- **Bubonic plague**: Bacterial growth in blood and lymph
- **Septicemia plague**: Septic shock
- **Pneumonic plague**: Bacteria in the lungs
The Black Death

Fig 23.11
Femoral bubo: Most common site of tender, swollen lymph node in patients with plague.
Bipolar staining: Dark stained bipolar ends in Wright's stain (blood from plague victim)
Lyme Disease

Zoonosis caused by *Borrelia burgdorferi*

Reservoir: mice, deer; Vector: *Ixodes* ticks

3 stages with various symptoms

1. **Early localized stage:** Bull’s eye rash = erythema (chronicum) migrans ECM; flu-like symptoms

2. **Early disseminated stage:** Heart and Nervous system symptoms; also skin and joints affected

3. **Late stage:** Chronic arthritis
Diagnosis

- Symptoms alone: often misdiagnosis
- In most cases not possible to isolate and culture *B. burgdorferi* → **indirect serological tests** (ELISA and Western blot)
- PCR

Prevention

Treatment in early stages!
Ixodes scapularis / pacificus

Ixodes pacificus
Established* and reported** distribution of the Lyme disease vectors Ixodes scapularis (I. dammini) and Ixodes pacificus, by county, United States. 1907-1996

*at least 6 ticks or 2 life stages (larvae, nymphs, adults) identified.
**at least 1 tick identified.
Life Cycle of the Tick

A. The female lays her eggs after dropping from the animal host.

B. The eggs hatch in the soil, and tick larvae emerge.

C. The tick larvae infest deer mice and feed on their blood, thereby becoming infected.

D. The infected larvae leave the mice and overwinter in dry leaves.

E. In the spring the infected larvae become nymphs.

F. The infected nymphs feed on animals or humans, and transmit Lyme disease.

G. The infected nymphs become adults.

H. The adults feed in the fur of deer, and mate to complete the cycle.

Compare to Fig 23.13a
Ehrlichiosis

First described in 1986

Caused by *Ehrlichia* species and transmitted by *Ixodes* ticks – diseases of animals and humans

Obligately intracellular (in white blood cells)

- **Monocytic Ehrlichiosis** (HME)
- **granulocytic Ehrlichiosis** (HGE)

Nonspecific symptoms (similar to other diseases)
HME and HGE

Reported cases, granulocytic (G) and monocytic (M)

No reported cases

HME and HGE
Lyme Disease and Ehrlichiosis

Female tick

Male tick

Avoid tick bites by wearing proper clothing
Rocky Mountain Spotted Fever (RMSF)

- *Rickettsia rickettsii*
- Zoonosis –
- Reservoir: mammals
- Vector: ticks
- Characteristic hemorrhagic rash – maculopapular – starts on palms and soles (unlike measles!)
- Can damage vital organs
Rocky Mountain Wood Tick (*Dermacentor andersoni*)
Red structures indicate immunohistological staining of *Rickettsia rickettsii* in endothelial cells of a blood vessel from a patient with fatal RMSF.
Figure 23.16

Spotted Fevers (Rocky Mountain Spotted Fever)

1-10  11-100  101-500  >500
Rocky Mountain Spotted Fever

Doc -- PLEASE don't miss this one!

The rash is usually absent at the onset, and may not appear.

"The usual" antibiotics that kill most bugs don't affect RMSF.

Easy to treat; often fatal if missed!
Infectious Mononucleosis
Viral Hemorrhagic Fevers
Infectious Mononucleosis

- “Kissing disease” – caused by Epstein-Barr virus (EBV) of Herpesviridae, also known as HHV-4
- Well-established relationship between HHV-4 and oncogenesis (Burkitt’s Lymphoma etc.)
- Virus multiplies in parotid glands and is present in saliva. It causes the proliferation of atypical lymphocytes (life-long infection) – Transmission via saliva
- Most people (~95%) infected. Childhood infection usually asymptomatic. Adolescent infection → Mononucleosis.
- Characteristic triad: fever, pharyngitis, and lymphadenopathy (+spleno- and hepatomegaly) lasting for 1 to 4 weeks.
Swollen lymph nodes, sore throat, fatigue and headache are some of the symptoms of mononucleosis. It is generally self-limiting and most patients can recover in 4 to 6 weeks without medications.
Young adults present with fever, pharyngitis, lymphadenopathy, and tonsillitis.
- Proliferation of infected B cells results in massive activation and proliferation of $T_c$ cells (CD8 cells) → characteristic lymphoid hyperplasia.

- Transformation of B cells to immortal plasmacytoid cells → secrete a wide variety of IgMs = heterophile antibodies (Monospot test)

- Commercially-available test kits are 70-92% sensitive and 96-100% specific

"Downy cell": lymphocytes infected by EBV or CMV in infectious mononucleosis. Cytoplasmic rim is intensely blue and has tendency to "stream" around adjacent red cells.
Pathogenesis of infectious mononucleosis

EB virus attaches to and infects epithelium of the throat, where it replicates and causes pharyngitis.

Virions enter the lymphatic vessels and are carried to the lymph nodes. Some virions escape the lymph node trap and are carried to the bloodstream.

Virions attach specifically to B lymphocytes and infect them, producing either latent or productive infections.

The infected B lymphocytes actively replicate and differentiate into cells producing random immunoglobulins, including heterophile antibody.

Productively infected B cell

Activated lymphocyte

T cells respond to infection and destroy the lymphocytes replicating EB virus.

Latently infected B cell

Latently infected B lymphocytes become immortal. They are not attacked by T cells.
Viral Hemorrhagic Fevers

- Enveloped RNA viruses: Arenaviruses, filoviruses, bunyaviruses, and flaviviruses
- Viruses geographically restricted to where their host species live
- For some viruses, after accidental transmission from host, humans to human transmission
- Human cases or outbreaks sporadic and irregular. Not easily predictable

- **Marburg VHF:** 1967 outbreak in Marburg (D) – imported from Africa; Mortality rate 25%
- **Ebola HF:** 1995 major outbreaks in Zaire and Sudan; Mortality rate 50 – 90%
Caused by arbovirus (flaviviridae) transmitted by mosquitoes

Direct damage to liver and heart $\rightarrow$ jaundice, hemorrhaging, weak heart $\rightarrow$ circulatory and kidney failure

African and American tropical jungles

Diagnosis: test for presence of virus-neutralizing antibodies

No treatment Highly effective attenuated vaccine
Hantavirus Pulmonary Syndrome (HPS)

Korean hemorrhagic fever caused by Hantaan virus of *Bunyaviridae*

HPS first reported in US in spring of 1993.

Transmission through urine, droppings, or saliva of infected rodents → humans breathe in aerosolized virus. No person to person transmission in US

Sudden respiratory failure

Mortality rate > 35%
Hanta Virus Cases

Total Cases (N = 289 in 31 States)

Hanta virus
Risk factor: contact with deer mouse droppings
PROTOZOAN DISEASES OF THE CARDIOVASCULAR AND LYMPHATIC SYSTEMS

- American Trypanosomiasis (Chagas’ Disease)
- Toxoplasmosis
- Malaria
- Babesiosis
American Trypanosomiasis or Chagas Disease

*Trypanosoma cruzi*

**Reservoir:** Rodents, opossums, armadillos

**Vector:** night feeding reduviid bugs (kissing bugs)

**Symptoms** in 1% of infected. Acute phase (fever etc.) to chronic phase (heart damage)

**Antigenic variation** $\Rightarrow$ persistent evasion of immune system

$\Rightarrow$ Cyclic parasitemia

(7-10 days)
Course of trypanosome infection: emergence of variant surface glycoproteins (VSG) - Host antibodies indicated with Y's.
Millions in Latin America affected. No cure and little effective treatment

**Romaña's sign:** pathogonomic, early sign of Chagas disease.

→ Unilateral severe conjunctivitis, swelling of eyelid, inflammation of tear gland, swelling of regional lymph nodes.
Toxoplasmosis

*Toxoplasma gondii*

> 60 mio people infected in US (mostly asymptomatic)

Zoonosis – Transmission via undercooked meat, cat feces, drinking water. Flu-like symptoms

Can cross placenta $\Rightarrow$ Congenital risk (TORCH) $\Rightarrow$ brain damage or vision problems

Risk of new infection or reactivation in the immunosuppressed

*T. gondii* undergoes sexual reproduction in the intestinal tract of domestic cats, and oocysts are eliminated in cat feces.

Toxoplasmosis can be identified by serological tests, but interpretation of the results is uncertain.
The *Toxoplasma gondii* life cycle

**Host (e.g. domestic cat) in which sexual cycle occurs**

- **Ingestion of tissue cysts**
- **Invasion of enterocytes: rounds of division**
- **Formation of microgametocytes and macrogametocytes**
- **Oocyst formation and defecation**
- **Sporozoite formation**

**Carnivorousm**

- **Conversion to slowly dividing bradyzoites in tissue cysts**
- **Ingestion by secondary host (e.g. mouse)**
- **Sporozoite differentiation to rapidly dividing tachyzoites**

**Chronic infection**

- **Carnivorousm and nonsexual propagation**
- **Naive host (e.g. rat)**

**Acute infection**

- **Congenital transmission to fetuses**

*Compare to Fig. in book*
Malaria

- Four species of Plasmodium: *P. falciparum* (malignant)
- Vector: *Anopheles* mosquito
- Worldwide 300-500 million cases; ~1.5 – 3 million people die; ~1,200 cases in US
- *Plasmodium* infects red blood cells ⇝ microscopic diagnosis
- Symptoms: chills, fever, vomiting, headache; at intervals of 2 to 3 days
- New drugs are being developed as the protozoa develop resistance to drugs such as chloroquine.
Microscopic Diagnosis

(a) Merozoites being released from lysed RBC.

(b) Malarial blood smear; note the ring forms.
Malaria

(a) Areas where malaria was endemic as recently as 1912

(b) Graph showing reported cases of malaria in the United States, 1967 to (*) the first 26 weeks of 2005.

Returning Vietnam veterans

Foreign immigration from malaria-endemic countries in Southeast Asia
Malaria Transmission Cycle

1. Plasmodium sporozoites
2. 1st Vector
3. Initial human host
4. Liver infection
5. Blood infection
6. 2nd Vector
7. Next human host
8. In utero transmission

Compare to Fig 12.19
Distribution of Malaria

- No malaria reported
- Chloroquine-sensitive species
- Chloroquine-resistant species
- Chloroquine and mefloquine resistance
Babesiosis

*Babesia microti*

Vector *Ixodes* tick - Zoonosis

Hemoprotezoan → rupture of RBCs → hemolytic anemia

In malaria-endemic areas, misdiagnosis as *Plasmodium*
Schistosomiasis / Bilharzia(sis)

- *Schistosoma mansoni*, *S. haematobium*, and *S. japonicum*
- 250 million people infected worldwide
- Cercaria penetrates skin when exposed to contaminated water → worms grow inside blood vessels and produce eggs → eggs travel to liver (liver damage), intestine or bladder.
- Treatment available *(praziquantel)*
Other Schistosomes: Swimmer’s Itch or Cercarial Dermatitis

**Schistosome cercaria** accidentally enters human skin (bird is definitive host for adult parasite)

Almost every state in US (Most predominant in the north). Also in more than 30 countries.

Disappears without treatment (~ 7 days) – no internal organs involved
Parasites die after entering dermatitis in previously sensitized individuals. Sensitivity rarely disappears; usually gets worse in subsequent exposures.

Widely scattered from Michigan lakes to Alaska.
the end