I. Rickettsiaceae

A. Disease/Etiologic agent
   1. Rocky Mountain Spotted Fever: *Rickettsia rickettsii*
   2. Rickettsialpox: *R. akari*
   3. Epidemic typhus (louse-borne typhus): *R. prowazekii*
      Brill-Zinsser disease: *R. prowazekii*
   4. Murine typhus: *R. typhi*
   5. Scrub typhus: *Orientia tsutsugamushi*

B. Typical Rickettsiaceae Family Characteristics

   Morphology and structure:
   1. Small (0.3 to 0.5 \( \mu \text{m} \))
   2. Gram negative
      a. LPS present (weak or no endotoxin activity)
      b. Peptidoglycan (minimal in some cases)
   3. No flagella
   4. Best visualized with Giemsa stain of infected cells

   Growth and metabolism:
   1. Division occurs through binary fission (transverse septum)
   2. Slow growth: generation time is 8 to 10 hours in cell culture at 34°C
   3. Obligate intracellular pathogens
      a. Use host ATP, coenzyme A, nicotinamide adenine dinucleotide and available
         amino acids
      b. Can synthesize their own ATP

   Pathogenesis:
   1. Bacteria enter by phagocytosis
      a. Bind host receptors
   2. Initially in membrane-bound vesicle
      a. Escape aided by phospholipase A
   3. Some can spread from cell to cell
      a. Those that move intracellularly are released through cytoplasmic projections
      b. Growth of others such as *R. prowazekii* eventually lyses the eukaryotic cell
   8. Outside the host cell, the bacteria are unstable and die quickly
      a. Infectivity of bacteria decreases as time outside the host increases

Epidemiology:
   1. Spread by insect vectors
      a. Ticks: RMSF
      b. Mites: Rickettsialpox, Scrub typhus
      c. Lice: Epidemic typhus
      d. Fleas: Murine typhus
2. Animal reservoirs
   a. Rodents: RMSF, Rickettsialpox, Murine typhus
   b. Dogs: RMSF
   c. Flying squirrels: Epidemic typhus

C. *Rickettsia rickettsii* (Spotted Fever group)

1. **Disease:** Spotted Fever group: Rocky Mountain Spotted Fever
   a. Acute febrile illness transmitted by ticks
   b. Most severe of the spotted fever group--25% mortality if untreated

2. **Clinical features**
   a. Early: High fever and severe headache
   b. Rash, toxicity, mental confusion, and myalgia (sore muscles)
   c. Rash most characteristic feature
      i. Rash present particularly on hands and feet
      ii. Rash moves from extremities to trunk of body
   d. Incubation period between tick bite and onset of illness usually 2 to 7 days, but may be upwards of two weeks

3. **Epidemiology**
   a. World wide distribution
   b. In U.S., most common rickettsial disease (about 2000 cases annually)
   c. Most cases now reported in the Southeast Atlantic and South Central states (North Carolina, Oklahoma, Arkansas, Tennessee, Missouri)
   d. Transmitted by ticks
      i. *Dermacentor andersoni* (wood tick)
      ii. *Dermacentor variabilis* (American dog tick)
      iii. *Rhipiephalus sanguineus* (brown dog tick)
   e. Occurs in association with residential and recreational exposure to wooded areas where infected ticks exist
   f. Illness usually seen between April and September
   g. Maintained in the tick population by passage from tick to tick through transovarian transmission.
   h. Small rodents and dogs may serve as a reservoir for tick infection

4. **Pathology**
   1. Cells infect the vascular endothelium using OmpA after delivery by insect bite
   2. Primary lesion: vasculitis
      a. Bacteria multiply in **endothelial** cells lining small blood vessels.
      b. Cells become swollen and necrotic
      c. Thrombosis (clotting) of the vessel, leading to rupture and necrosis
   3. Vasculitis occurs in many organs
      a. Vascular lesions are most prominent in the skin
      b. Most serious in the adrenal glands
5. **Diagnosis**
   a. Clinical symptoms, epidemiology
   b. Positive results for IFA
      i. Initial titer of 1:64 or higher
      ii. 4-fold rise in antibody titer
      iii. Antibody levels arise 2-3 weeks after onset
c. Microimmunofluorescence (MIF)
d. PCR with gene targets such as *ompA*, *ompB*

6. **Treatment**
   a. Tetracycline
   b. Fluoroquinolones
   c. Chloramphenicol

7. **Prevention**
   a. No vaccine
   b. Avoidance or reduction of tick contact
   c. Frequent removal of attached ticks: infectivity/transmission requires extended period of time.
   d. Control is virtually impossible because the tick reservoir can survive for as long as 4 years without feeding!

D. **Rickettsia akari** (Spotted Fever group)

1. **Disease**: Spotted Fever group: Rickettsialpox
   a. Mild disease with a rash resembling that of varicella

2. **Clinical features**
   a. Phase 1
      i. A firm red papule appears at the site of the bite
      ii. Papule develops into deep-seated vesicle then black eschar
      iii. Bacteria spread systemically
   b. Phase 2
      i. After 9-14 days, high fever, severe headache, chills/sweats, myalgias, photophobia develop
      ii. A vesicular rash develops (small, blister like lesions filled with clear fluid).
   c. Self-limiting after 1 week; no deaths have been reported

4. **Epidemiology**
   a. Found among inhabitants of apartments in northern USA
   b. Also occurs in Russia, Africa, and Korea
   c. Vector is blood sucking mites
   d. Mites are found on mice
   e. Transovarian transmission occurs
   f. Mites are probably true reservoir as well as vector

5. **Prevention**
a. Elimination of rodents and their parasites from human domiciles

E. *Rickettsia prowazekii* (Typhus group)

1. **Disease**: Epidemic typhus (Primary Louse-borne Typhus Fever)
   a. A severe febrile disease

2. **Clinical features**
   a. Fever, headache and rash begin 1 to 2 weeks after the bite
   b. Fever lasts two weeks
   c. Maculopapular rash begins first on the trunk and then spreads centripetally to the extremities (opposite to Rocky Mountain Spotted fever)
      i. Macular: flat lesions detected because of a change in color or texture of the lesion
      ii. Papular: lesions, which are raised and well circumscribed
   d. Headache, malaise, myalgia are prominent
   e. More fatal in patients >40 years old
   f. Complications include myocarditis and central nervous system dysfunction
   g. Fatality from 20 to 30% in untreated disease

3. **Epidemiology**
   a. Potentially world-wide
   b. Disease is present in Central, South America, Africa; only sporadically in U.S. rural areas
   c. Disease associated with crowded, unsanitary conditions that favor the spread of body lice.
   d. Seasonal: peaks in winter
   e. Transmission by *Pediculus humanus corporis* and *Pediculus humanus capitis* (body louse)
   f. Organisms are present in the feces of the infected lice and enter through the bite wound or skin abrasions
   g. Lice die after 2-3 weeks, thus preventing transovarian transmission
   h. Bacteria remain viable in lice feces
   i. Reservoirs include humans and flying squirrels, which are present in Eastern and mid-western U.S.

4. **Diagnosis**
   a. based on clinical presentation, MIF

5. **Treatment**
   a. Tetracycline or chloramphenicol combined with louse control
   b. Vaccine available for high risk population

6. **Recrudescent Typhus (Brill’s disease)**
   a. Relapse of louse-borne typhus appearing 10-40 years after the primary attack
   b. Milder and less often fatal; partial immunity may still be present
c. *Rickettsia* persist for many years in the lymph nodes of an individual without any symptoms being manifest
d. Humans themselves are thus the reservoir of the *Rickettsia* of epidemic typhus

**F. *Rickettsia typhi* (Typhus Group)**

1. **Disease**: Endemic (murine) typhus

2. **Clinical features**
   a. Incubation period 1-2 weeks
   b. Symptoms appear abruptly
   c. Fever, severe headache, chills, myalgia, nausea
   d. Rash in 50% of cases, typically restricted to the chest and abdomen, but may extend to palms and soles.

3. **Epidemiology**
   a. 50-100 cases annually in U.S.—Gulf states and Southern California
   b. Found in temperate and subtropical coastal areas of Africa, Asia, Australia, Europe, and South America
   c. Rat flea primary vector, cat flea in the U.S.
   d. Rodents are reservoirs
   e. Most cases occur during warm months

4. **Diagnosis**
   a. Clinical features
   b. Positive IFA
      i. Single titer of at least 1:128
      ii. 4-fold increase in titer
      iii. Significant titers detectable within 1-2 weeks

5. **Treatment**
   a. Tetracycline, doxycycline, chloramphenicol
   b. No vaccine is available

**G. *Orientia tsutsugamushi***

1. **Disease**: Scrub Typhus

2. **Clinical features**
   a. Resembles epidemic typhus clinically
   b. Typical initial lesion, a necrotic eschar at the site of the bite on the extremities, develops in only 50 to 80% of the cases.
   c. Generalized lymphadenopathy (abnormal enlargement of lymph nodes) and lymphocytosis (above normal increase in lymphocytes) are common
   d. Cardiac and cerebral involvement may be severe
3. **Epidemiology**
   a. Mites that infest rodents are the reservoir and vectors.
   b. Passaged to progeny via infected ova.
   c. Found in the southwest Pacific, Southeast Asia, and Japan

4. **Treatment and prevention**
   a. Fever responds to treatment with tetracycline, doxycycline or chloramphenicol
   b. Untreated patients: fever disappears after 2-3 weeks
   c. Prevention
      i. No vaccine
      ii. Clearing areas in which rats and mites live
      iii. Protective clothing

II. **Anaplasmataceae**

   A. *Anaplasma phagocytophilum, Ehrlichia ewingii, and Ehrlichia chaffeensis*

   1. **Diseases**
      a. Human anaplasmosis (HA), caused by *Anaplasma phagocytophilum* or *Ehrlichia ewingii*
      b. Human monocyte ehrlichiosis (HME), caused by *Ehrlichia chaffeensis*
      c. Diseases are associated with infected blood cells
      d. Severe or fatal illness

   2. **Clinical features and Pathology**
      a. Clinically similar to Rocky Mountain Spotted Fever
      b. Typically **no rash**.
      c. Fever, chills, headache, myalgia, nausea or vomiting
      d. Weight loss
      e. Mortality in less than 5% of patients
      f. Leukopenia, thrombocytopenia, and elevated serum transaminases develop in majority of patients
      g. Mortality low but >50% require hospitalization
      h. Gastrointestinal symptoms in <50%
      i. Human anaplasmosis (HA)
         i. Infection primarily of bone marrow myeloid cells (neutrophils)
      j. Human monocyte ehrlichiosis (HME)
         i. Monocytes primarily infected
         ii. late-onset rash in 30-40%
      k. Ehrlichia infect circulating leukocytes
         i. Bacteria lack peptidoglycan and LPS
         ii. Form cytoplasmic inclusions called morulae
            a. Small elementary bodies (0.2-0.4 uM)
            b. Large reticulate bodies (0.8-1.5 uM)
            c. Prevent lysosomal fusion
            d. Grow until host cell lyses
5. **Epidemiology**
   a. HME vector is Lone Star tick (*Amblyomma Americanum*); white-tailed deer (and the domestic dog) are reservoirs
   b. Human anaplasmosis vector is *Ixodes* tick; reservoirs include chipmunks, mice, voles
   c. Transmission within 6 hours
   d. Transovarian transmission is inefficient
   e. HME found in U.S. predominantly in southeastern, mid-Atlantic and south central states; OK has high rate of incidence
   f. Human anaplasmosis found in U.S. primarily in northern and central midwestern states and northeast and central Atlantic states.
   g. >90% of cases between April and October

6. **Diagnosis**
   a. History of tick exposure during month prior to onset
   b. Clinical symptoms
   c. Presence of morulae in white blood cells
   d. IFA; increase in antibody titer after 2 weeks; used for confirmation
   e. PCR in reference laboratories

8. **Treatment**
   a. Doxycycline should be used
   b. Penicillin, chloramphenicol, macrolides not effective
   c. Rifampin for pregnant women

**III. Coxiellaceae**

A. Q-Fever

1. **Cause:** *Coxiella burnetii*

2. **Clinical features**
   a. Most human infections are NOT apparent
   b. There is no rash
   c. 9 to 20 days after inhalation, there is an abrupt onset of fever, chills, and headache.
   d. A mild, dry, hacking cough and patchy interstitial pneumonia may or may not be present.
   e. Complications, though rare, include infective endocarditis
   f. Fatalities are rare

3. **Epidemiology**
   a. Transmission from animals to humans by inhalation rather than by arthropod bite
   b. World-wide distribution
   c. Carried by mammals such as cattle, sheep, and goats
   d. Disease occurs among those exposed to infected animals or their products,
particular workers involved with slaughtering
  e. Infection is believed to typically occur through inhalation of dust contaminated with *Coxiella* or from aerosols in slaughterhouses

4. **Pathogenesis**
   a. *C. burnetii* primarily replicates in the Coxiella-containing vacuole (CCV) because *C. burnetii* requires low pH
   b. *C. burnetii* forms endospores and thus is resistant to drying and other environmental conditions
   c. Phase variation of LPS correlates with more and less virulent forms of *C. burnetii*
   d. High antibody titers lead to the formation of immune complexes

5. **Diagnosis**
   a. Serology
      i. IgM titer of 1:50
      ii. IgG titer of 1:200
      iii. 4-fold rise in antibody titer
      iv. IgG titer positive after 12 weeks
   b. PCR

6. **Treatment and prevention**
   a. Tetracycline, doxycycline for acute infections
   b. Combination of antibiotics for chronic infections
   c. Vaccines have been developed, only effect in unexposed

**Study questions:**
1. What cell type does *R. rickettsii* infect? What about *Ehrlichia? Anaplasma?* How does *Coxiella burnetii* pathogenesis differ from Rickettsial organisms such as *Rickettsia rickettsii*?

2. For which diseases is rash a prominent clinical feature? What are the characteristics of the rash for each of these diseases?

3. For the disease that lack rash as a prominent symptom, what clinical features would permit a presumptive diagnosis?


5. Which organisms replicate in a phagosome? Free in the cytoplasm? Which spread intracellularly via actin polymerization?

**Practice question:**
After returning from an extended stay at her Aunt Sarah's cattle ranch in Oklahoma, 12-year old Susie complains of flu-like symptoms: fever, headache, chills, myalgia, and a persistent cough. You see no signs of rash. Laboratory cultures for bacteria came back negative. Lab results
indicated normal white blood cells. You conclude that the causative agent of this disease was transmitted to Susie:

A. By a bite from a blood sucking mite
B. Through exposure to the wood tick *Dermacentor andersoni*
C. By breathing dust from the cattle.
D. From Aunt Sarah’s persistent cough
E. Through a louse bite

Answer: C