



BLOOD & LYMPHATIC SYSTEM MICROBIOLOGY

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Gram-Negative Rods Related to Animal Sources

Introduction

- ❑ Zoonoses are human diseases caused by organisms that are acquired from animals.
- ❑ There are bacterial, viral, fungal, & parasitic zoonoses.
- ❑ Some zoonotic organisms are acquired directly from the animal reservoir, whereas others are transmitted by vectors, such as mosquitoes, fleas, or ticks.
- ❑ There are four medically important gram-negative rods that have significant animal reservoirs: *Brucella* species, *Francisella tularensis*, *Yersinia pestis*, & *Pasteurella multocida*

Table 20–1 Gram-Negative Rods Associated with Animal Sources

Species	Disease	Source of Human Inflection	Mode of Transmission from Animal to Human	Diagnosis
<i>Brucella</i> species	Brucellosis	Pigs, cattle, goats, sheep	Dairy products; contact with animal tissues	Serology or culture
<i>Francisella tularensis</i>	Tularemia	Rabbits, deer, ticks	Contact with animal tissues; ticks	Serology
<i>Yersinia pestis</i>	Plague	Rodents	Flea bite	Immunofluorescence or culture
<i>Pasteurella multocida</i>	Cellulitis	Cats, dogs	Cat or dog bite	Wound culture

Bacterial Zoonosis

Brucella

Anthrax

Plague

Pasteurella

Tularemia

leptospira

Lyme

Disease

Brucella species cause brucellosis
(undulant fever)

Important Properties

- Brucellae are small gram-negative rods without a capsule.
- The 3 major human pathogens & their animal reservoirs are
 1. *Brucella melitensis* (goats & sheep)
 2. *Brucella abortus* (cattle)
 3. *Brucella suis* (pigs.)

Pathogenesis

- **The organisms enter the body either by:**
 - **ingestion of contaminated milk products or through**
 - **the skin by direct contact in an occupational setting such as an abattoir.**
- **They localize in the reticuloendothelial system, namely, the lymph nodes, liver, spleen, & bone marrow.**
- **Many organisms are killed by macrophages, but some survive within these cells, where they are protected from antibody.**

Pathogenesis

- **The host response is granulomatous, with lymphocytes & epithelioid giant cells, which can progress to form focal abscesses.**
- **The mechanism of pathogenesis of these organisms is not well defined, except that endotoxin is involved.**
- **No exotoxins are produced.**

Epidemiology

- **Imported cheese made from unpasteurized goats' milk produced in either Mexico or the Mediterranean region has been a source of *B. melitensis* infection in the USA.**
- **The disease occurs worldwide but is rare in the USA because pasteurization of milk kills the organism.**

Clinical Findings

- **After an IP of 1 to 3 weeks, nonspecific symptoms such as fever, chills, fatigue, malaise, anorexia, & weight loss occur.**
- **The onset can be acute or gradual.**
- **The undulating (rising-&-falling) fever pattern that gives the disease its name occurs in a minority of patients.**
- **Enlarged lymph nodes, liver, & spleen are frequently found.**

Clinical Findings

- Pancytopenia occurs
- *B. melitensis* infections tend to be more severe & prolonged, whereas those caused by *B. abortus* are more self-limited.
- Osteomyelitis is the most frequent complication
- Secondary spread from person to person is rare

Laboratory Diagnosis

- Recovery of the organism requires the use of enriched culture media & incubation in 10% CO₂
- The organisms can be identified by using a slide agglutination test with *Brucella* antiserum, & the species can be identified by biochemical tests
- If organisms are not isolated, analysis of a serum sample from the patient for a rise in antibody titer to *Brucella* can be used to make a diagnosis.
- In the absence of an acute-phase serum specimen, a titer of at least 1:160 in the convalescent-phase serum sample is diagnostic.

Treatment

- **The treatment of choice is tetracycline plus rifampin. There is no significant resistance to these drugs.**
- TMP-SMZ has been effective in this population, either as monotherapy or as part of combination therapy with rifampin or gentamicin.
- The most common recommendation is for rifampin, either alone or in combination with TMP-SMZ.
- It should be kept in mind that the use of TMP-SMZ by the end of pregnancy is associated with [kernicterus](#).

Prevention

- **Pasteurization of milk,**
- **Immunization of animals**
- **Slaughtering of infected animals.**
- **There is no human vaccine.**

Francisella tularensis

Disease

- ***Francisella tularensis* causes tularemia.**

Important Properties

- *F. tularensis* is a small, pleomorphic gram-negative rod.
- It has a single serologic type.
- There are 2 biotypes, A & B, which are distinguished primarily on their virulence & epidemiology.
- Type A is more virulent & found primarily in the USA, whereas type B is less virulent & found primarily in Europe.

Epidemiology

- ***F. tularensis* is remarkable in the wide variety of animals that it infects & in the USA.**
- **It is enzootic (endemic in animals) in every state, but most human cases occur in the rural areas of Arkansas & Missouri.**
- **It has been isolated from more than 100 different species of wild animals, the most important of which are rabbits, deer, & a variety of rodents.**
- **The bacteria are transmitted among these animals by vectors such as ticks, mites, & lice, especially the ticks that feed on the blood of wild rabbits.**

Pathogenesis & Epidemiology

- The tick maintains the chain of transmission by passing the bacteria to its offspring by the transovarial route.
- In this process, the bacteria are passed through ovum, larva, & nymph stages to adult ticks capable of transmitting the infection.

Epidemiology

Humans are accidental "dead-end" hosts who acquire the infection most often by:

- **being bitten by the vector**
- **having skin contact with the animal during removal of the hide (دلج ناويحلا).**
- **the organism is ingested in infected meat, causing GI tularemia, or is inhaled, causing pneumonia.**

There is no person-to-person spread.

Pathogenesis

- **The organism enters through the skin, forming an ulcer at the site in most cases. It then localizes to the cells of the reticuloendothelial system, & granulomas are formed.**
- **Caseation necrosis & abscesses can also occur.**
- **Symptoms are caused primarily by endotoxin.**
- **No exotoxins have been identified.**

Clinical Findings

- **Presentation can vary from**
- **sudden onset of an influenza-like syndrome to**
- **prolonged onset of a low-grade fever & adenopathy.**

- **%75of cases are the “ulcer-glandular” type, in which the site of entry ulcerates & the regional lymph nodes are swollen & painful.**

- **Less frequent forms of tularemia include glandular, oculo-glandular, typhoidal, GI, & pulmonary.**

- **Disease usually confers lifelong immunity.**



***Tularemia
lymphadenopathy***

Laboratory Diagnosis

- Attempts to culture the organism in the laboratory are rarely undertaken, because
 - there is a high risk to laboratory workers of infection by inhalation &
 - the special cysteine-containing medium required for growth is not usually available.
- The most frequently used diagnostic method is the agglutination test with acute- & convalescent-phase serum samples.
- Fluorescent-antibody staining of infected tissue can be used if available.

Treatment

- **Streptomycin is the drug of choice.**
- **There is no significant antibiotic resistance.**

Prevention

- **Prevention involves avoiding both being bitten by ticks & handling wild animals.**
- **There is a live, attenuated bacterial vaccine that is given only to persons, such as fur trappers, whose occupation brings them into close contact with wild animals.**
- **The vaccine is experimental & not available commercially but can be obtained from the U.S. Army Medical Research Command, Fort Detrick, Maryland.**
- **This & the bacillus of Calmette-Guérin (BCG) vaccine for tuberculosis are the only two live bacterial vaccines for human use.**

Yersinia Pestis



***Yersinia pestis*- Gram (-) bacillus**

Vectors - Rat & Flea

Bubonic Plague or the Black Death

- Epidemic swept thru Europe in the Middle Ages 13)th & 14th centuries(
 - 40million people were killed
 - About 1/3 of the population of the continen
- Etiological agent:
 - *Yersinia pestis* Gram (-) rod
- 2Vectors
 - Rat
 - Flea

Disease

- ***Yersinia pestis*** is the cause of plague, also known as the black death, the scourge of the Middle Ages.
- It is also a contemporary disease, occurring in the western USA & in many other countries around the world.
- Two less important species, *Yersinia enterocolitica* & *Yersinia pseudotuberculosis*,

Important Properties

- *Y. pestis* is a small gram-negative rod that exhibits bipolar staining, i.e., it resembles a safety pin, with a central clear area.
- Freshly isolated organisms possess a capsule composed of a polysaccharide–protein complex.
- The capsule can be lost with passage in the laboratory; loss of the capsule is accompanied by a loss of virulence.
- It is one of the most virulent bacteria known & has a strikingly low ID₅₀, i.e., 1 to 10 organisms are capable of causing disease.

Epidemiology

- **The plague bacillus has been endemic in the wild rodents of Europe & Asia for thousands of years but entered North America in the early 1900s, probably carried by a rat that jumped ship at a California port.**
- **It is now endemic in the wild rodents in the western USA, although 99% of cases of plague occur in Southeast Asia.**

Epidemiology

- The enzootic (sylvatic) cycle consists of transmission among wild rodents by fleas.
- In the USA, prairie dogs are the main reservoir.
- Rodents are relatively resistant to disease; most are asymptomatic.
- Humans are accidental hosts, & cases of plague in USA occur as a result of being bitten by a flea that is part of the sylvatic cycle.

Epidemiology

- **The urban cycle, consists of the transmission of the bacteria among urban rats, with the rat flea as a vector.**
- **This cycle predominates during times of poor sanitation, e.g., wartime, when rats proliferate & come in contact with the fleas in the sylvatic cycle.**

Pathogenesis & Epidemiology

- **The flea ingests the bacteria while taking a blood meal from a bacteremic rodent.**
- **The blood clots in the flea's stomach as a result of the action of the enzyme coagulase, which is made by the bacteria.**
- **The bacteria are trapped in the fibrin & proliferate to large numbers.**
- **The mass of organisms & fibrin block the proventriculus of the flea's intestinal tract, & during its next blood meal the flea regurgitates the organisms into the next animal.**

Pathogenesis

- **Because the proventriculus is blocked, the flea gets no nutrition, becomes hungrier, loses its natural host selectivity for rodents, & more readily bites a human.**
- **The organisms inoculated at the time of the bite spread to the regional lymph nodes, which become swollen & tender.**

Pathogenesis

- **These swollen lymph nodes are the buboes that have led to the name bubonic plague.**
- **The organisms can reach high concentrations in the blood (bacteremia) & disseminate to form abscesses in many organs.**
- **The endotoxin-related symptoms, including DIC & cutaneous hemorrhages, probably were the genesis of the term black death.**

Pathogenesis

- In addition to the sylvatic & urban cycles of transmission,
- Respiratory droplet transmission of the organism from patients with pneumonic plague can occur.

Pathogenesis

The organism has several factors that contribute to its virulence:

- 1. the envelope capsular antigen, called F-1, which protects against phagocytosis;**
 - 2. endotoxin;**
 - 3. exotoxin;**
 - 4. Two proteins are known as V antigen & W antigen.**
- The V & W antigens allow the organism to survive & grow intracellularly, but their mode of action is unknown.**
 - The action of the exotoxin is unknown.**

Pathogenesis

- **Other factors that contribute to the extraordinary pathogenicity of *Y. pestis* are a group of virulence factors collectively called Yops (Yersinia outer proteins.)**
- **These are injected into the human cell via type III secretion systems & inhibit phagocytosis & cytokine production by macrophages & neutrophils.**
- **For example, one of the Yops proteins (YopJ) is a protease that cleaves two signal transduction pathway proteins required for the induction of tumor necrosis factor synthesis.**
- **This inhibits the activation of our host defenses & contributes to the ability of the organism to replicate rapidly within the infected individual.**

Clinical Findings

- **Bubonic plague**
- **Is the most frequent form**
- **Begins with pain & swelling of the lymph nodes draining the site of the flea bite**
- **Systemic symptoms such as high fever, myalgias, & prostration.**
- **The affected nodes enlarge & become exquisitely tender. These buboes are an early characteristic finding.**

Clinical Findings

- **Septic shock & pneumonia**
- **The main life-threatening subsequent events**
- **Pneumonic plague Arise either from**
 - **inhalation of an aerosol or from**
 - **septic emboli that reach the lungs.**
- **Untreated bubonic plague is fatal in approximately half of the cases**
- **Untreated pneumonic plague is invariably fatal.**

Bubonic Plague Infection

- If untreated, about 50 % Mortality Rate
- If bacteria spread to the lungs, it becomes Pneumonic Plague & is now highly contagious (Almost a 99 % Mortality Rate)



Laboratory Diagnosis

- Smear & culture of blood or pus from the bubo is the best diagnostic procedure.
- Great care must be taken by the physician during aspiration of the pus & by laboratory workers doing the culture not to create an aerosol that might transmit the infection.
- Giemsa or Wayson stain reveals the typical safety-pin appearance of the organism better than does Gram stain.
- Fluorescent-antibody staining can be used to identify the organism in tissues.
- A rise in antibody titer to the envelope antigen can be useful retrospectively.

Treatment

- **The treatment of choice is a combination of streptomycin & tetracycline, although streptomycin alone can be used.**
- **There is no significant antibiotic resistance.**
- **In view of the rapid progression of the disease, treatment should not wait for the results of the bacteriologic culture.**
- **Incision & drainage of the buboes are not usually necessary.**

Prevention

- **Prevention of plague involves controlling the spread of rats in urban areas, preventing rats from entering the country by ship or airplane.**
- **Avoiding both flea bites & contact with dead wild rodents.**
- **A patient with plague must be placed in strict isolation (quarantine) for 72 hours after antibiotic therapy is started.**

Prevention

- Only close contacts need receive prophylactic tetracycline, but all contacts should be observed for fever.
- Reporting a case of plague to the public health authorities is mandatory.
- A vaccine consisting of formalin-killed organisms provides partial protection against bubonic but not pneumonic plague.
- This vaccine was used in the armed forces during the Vietnam war but is not recommended for tourists traveling to Southeast Asia.

Pasteurella

Pasteurella

- **Disease**
- *Pasteurella multocida* causes wound infections associated with cat & dog bites.
- **Important Properties**
- *P. multocida* is a short, encapsulated gram-negative rod that exhibits bipolar staining.

Pasteurella

- **Epidemiology**
- **The organism is part of the normal flora in the mouths of many animals, particularly domestic cats & dogs, & is transmitted by biting.**
- **About 25% of animal bites become infected with the organism, with sutures acting as a predisposing factor to infection.**
- **Most bite infections are polymicrobial, with a variety of facultative anaerobes & anaerobic organisms present in addition to *P. multocida*.**

Pasteurella

- **Pathogenesis**
- **Pathogenesis is not well understood, except that the capsule is a virulence factor & endotoxin is present in the cell wall.**
- **No exotoxins are made.**

Pasteurella

- **Clinical Findings**
- **A rapidly spreading cellulitis at the site of an animal bite is indicative of *P. multocida* infection.**
- **The IP is brief, usually less than 24 hours.**
- **Osteomyelitis can complicate cat bites in particular because cats' sharp, pointed teeth can implant the organism under the periosteum.**

Pasteurella

Laboratory Diagnosis

- The diagnosis is made by finding the organism in a culture of a sample from the wound site.

Treatment

- Penicillin G is the treatment of choice.
- There is no significant antibiotic resistance.

Prevention

- People who have been bitten by a cat should be given ampicillin to prevent *P. multocida* infection.
- Animal bites, especially cat bites, should not be sutured.

Bacillus anthracis

BACILLUS ANTHRACIS

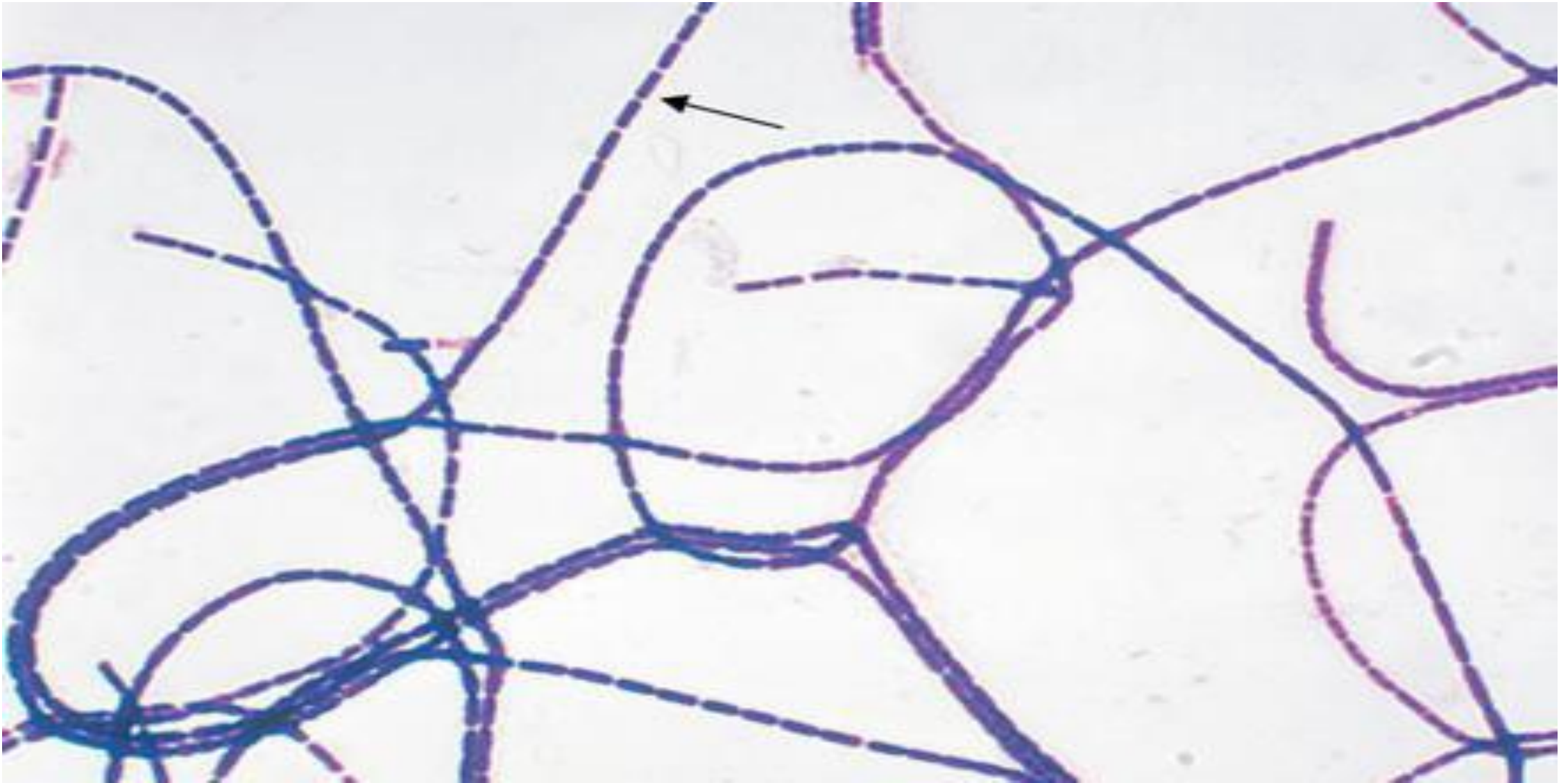
DISEASE

- *B. anthracis* causes anthrax, which is common in animals but rare in humans. Gm positive rods, spore forming
- Human disease occurs in 3 main forms:
 1. Cutaneous
 2. Pulmonary (inhalation)
 3. Gastrointestinal
- In 2001, an outbreak of both inhalation & cutaneous anthrax occurred in the USA.
- The outbreak was caused by sending spores of the organism through the mail.

BACILLUS ANTHRACIS

IMPORTANT PROPERTIES

- *B. anthracis* is a large gram-positive rod with square ends, frequently found in chains.
- Its antiphagocytic capsule is composed of D-glutamate. (This is unique—capsules of other bacteria are polysaccharides).
- It is non-motile, whereas other members of the genus are motile.
- Anthrax toxin is encoded on one plasmid & the polyglutamate capsule is encoded on a different plasmid.



Bacillus anthracis—Gram stain. Arrow points to one large "box car-like" gram-positive rod within a long chain

BACILLUS ANTHRACIS

TRANSMISSION

- Spores of the organism persist in soil for years.
- Cutaneous anthrax
- Humans are most often infected at the time of trauma to the skin, which allows the spores on animal products, such as hides, bristles, & wool, to enter.
- Pulmonary anthrax
- Spores can also be inhaled into the RT.
- GIT anthrax occurs when contaminated meat is ingested.

BACILLUS ANTHRACIS

TRANSMISSION

- Inhalation anthrax is not communicable from person-to-person, despite the severity of the infection.
- After being inhaled into the lung, the organism moves rapidly to the mediastinal lymph nodes, where it causes hemorrhagic mediastinitis.
- Because it leaves the lung so rapidly, it is not transmitted by the respiratory route to others.

BACILLUS ANTHRACIS

PATHOGENESIS

- Pathogenesis is based primarily on the production of two exotoxins, collectively known as anthrax toxin.
 1. Edema factor
 2. Lethal factor
- Each consist of two proteins in an A–B subunit configuration.
 - The B, or binding, subunit in each of the two exotoxins is protective antigen.
 - The A, or active, subunit has enzymatic activity.

BACILLUS ANTHRACIS

PATHOGENESIS

- **Edema factor, an exotoxin**
- **Is an adenylate cyclase that causes an increase in the intracellular concentration of cyclic AMP.**
- **This causes an outpouring of fluid from the cell into the extracellular space, which manifests as edema.**
- **)Note the similarity of action to that of cholera toxin(.**

BACILLUS ANTHRACIS

PATHOGENESIS

- **Lethal factor**
- **Is a protease that cleaves the phosphokinase that activates the mitogen- activated protein kinase (MAPK) signal transduction pathway.**
- **This pathway controls the growth of human cells, & cleavage of the phosphokinase inhibits cell growth.**

BACILLUS ANTHRACIS

PATHOGENESIS

- **Protective antigen forms pores in the human cell membrane that allows edema factor & lethal factor to enter the cell.**
- **The name protective antigen refers to the fact that antibody against this protein protects against disease.**

CLINICAL FINDINGS

CUTANEOUS ANTHRAX

- The typical lesion of cutaneous anthrax is a painless ulcer with a black eschar (crust, scab.)
- Local edema is striking.
- The lesion is called a malignant pustule.
- Untreated cases progress to bacteremia & death.

CLINICAL FINDINGS

PULMONARY ANTHRAX

- Pulmonary (inhalation) anthrax, also known as "wool sorter's disease",
- Begins with nonspecific respiratory tract symptoms resembling influenza, especially
- A dry cough
- Substernal pressure.
- Rapidly progresses to
- Hemorrhagic mediastinitis
- Bloody pleural effusions
- Septic shock
- Death

CLINICAL FINDINGS

PULMONARY ANTHRAX

- Although the lungs are infected, the classic features & X-ray picture of pneumonia are not present.
- Mediastinal widening seen on chest X-ray is an important diagnostic criterion.
- **Complications**
- Hemorrhagic mediastinitis & hemorrhagic meningitis are severe life-threatening complications.

CLINICAL FINDINGS

GASTROINTESTINAL ANTHRAX

- The symptoms of gastrointestinal anthrax include
- Vomiting
- Abdominal pain
- Bloody diarrhea

BACILLUS ANTHRACIS

LABORATORY DIAGNOSIS

- Smears show large, gram-positive rods in chains.
- Spores are usually not seen in smears of exudate because spores form when nutrients are insufficient, & nutrients are plentiful in infected tissue.
- Non-hemolytic colonies form on blood agar aerobically.
- A rapid diagnostic procedure is the **direct fluorescent antibody test** that detects antigens of the organism in the lesion.
- Serologic tests, such as an **ELISA test for antibodies**, require acute & convalescent serum samples & can only be used to make a diagnosis retrospectively.

BACILLUS ANTHRACIS
LABORATORY DIAGNOSIS

- In case of a bioterror attack,
- Rapid diagnosis can be performed using polymerase chain reaction (PCR)

BACILLUS ANTHRACIS

TREATMENT

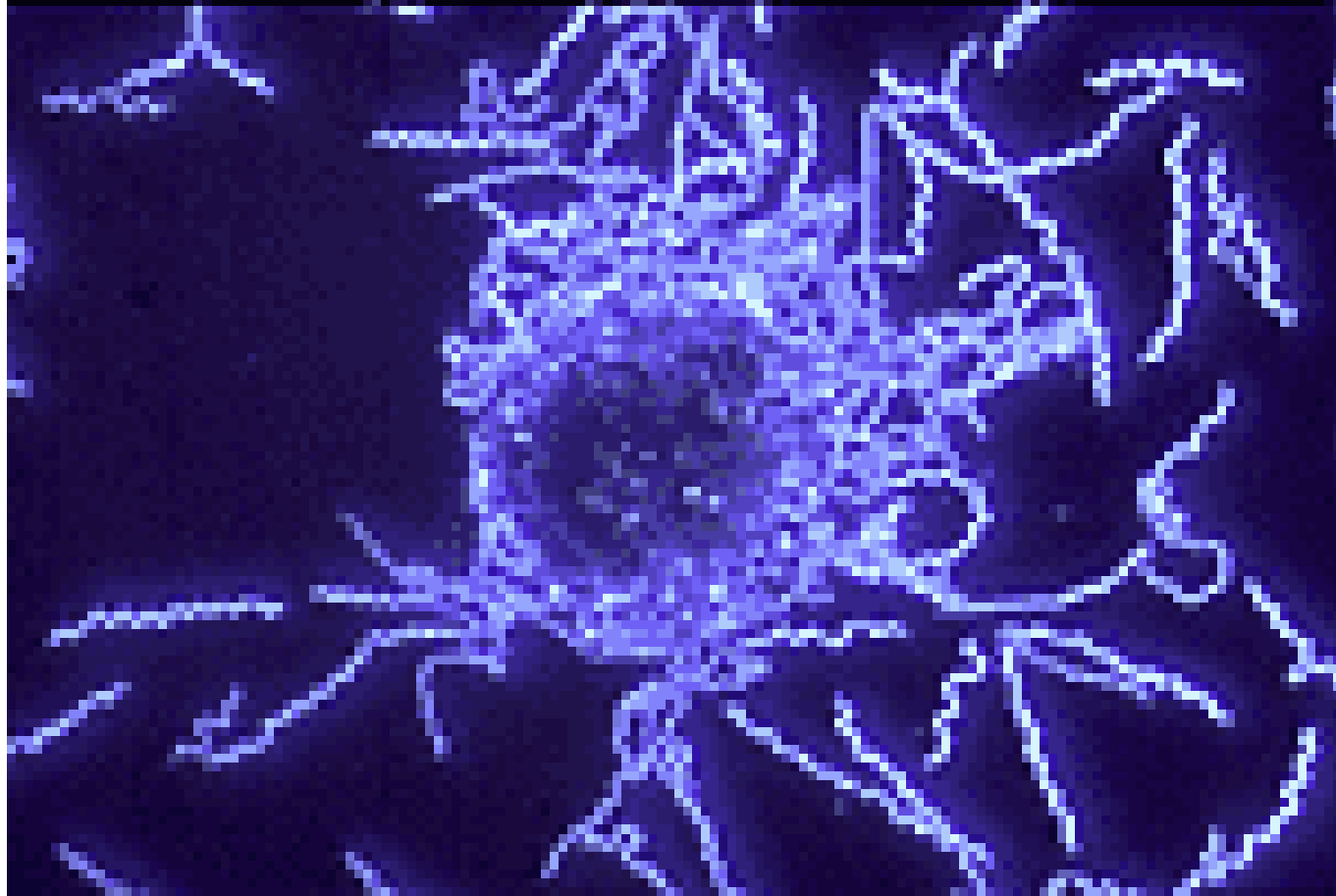
- **Ciprofloxacin is the drug of choice.**
- **Doxycycline is an alternative drug.**
- **No resistant strains have been isolated clinically.**

BACILLUS ANTHRACIS

PREVENTION

- Ciprofloxacin or doxycycline was used as prophylaxis in those exposed during the outbreak in the USA in 2001
- People at high risk can be immunized with cell-free vaccine containing purified protective antigen as immunogen.
- The vaccine is weakly immunogenic, & six doses of vaccine over an 18-month period are given.
- Annual boosters are also given to maintain protection.
- Incinerating animals that die of anthrax, rather than burying them, will prevent the soil from becoming contaminated with spores.

Borrelia



Borrelia burgdorferi

Borrelia

- ✿ ***Borrelia* species are irregular, loosely coiled spirochetes that stain readily with Giemsa & other stains.**
- ✿ **They can be cultured in bacteriologic media containing serum or tissue extracts.**
- ✿ **They are transmitted by arthropods.**
- ✿ **They cause two major diseases, Lyme disease and relapsing fever.**

Borrelia burgdorferi

Lyme Disease

 ***Borrelia burgdorferi* causes Lyme disease (named after a town in Connecticut.)**

 **Lyme disease is also known as Lyme borreliosis.**

 **The disease occurs worldwide**

 **Lyme disease is the most common tick-borne disease in the USA.**

 **It is also the most common vector-borne disease in the USA.**

Borrelia burgdorferi

✧ Important Properties

- ✧ *B. burgdorferi* is a flexible, motile spirochete that can be visualized by darkfield microscopy & by Giemsa & silver stains.
- ✧ It can be grown in certain bacteriologic media, but routine cultures obtained from patients (e.g., blood, spinal fluid) are typically negative.
- ✧ In contrast, culture of the organism from the tick vector is usually positive.

Transmission

- ✿ *B. burgdorferi* is transmitted by tick bite.
- ✿ The main reservoir of the organism consists of small mammals, especially the white-footed mouse, upon which the nymphs feed.
- ✿ Large mammals, especially deer, are an obligatory host in the tick's life cycle but are not an important reservoir of the organism.
- ✿ The nymphal stage of the tick transmits the disease more often than the adult & larval stages do. Nymphs feed primarily in the summer, which accounts for the high incidence of disease during the months of May to September.

Transmission

- ✦ The tick must feed for 24 to 48 hours to transmit an infectious dose.
- ✦ This implies that inspecting the skin after being exposed can prevent the disease. However, the nymphs are quite small & can easily be missed.
- ✦ There is no human-to-human spread.

Epidemiology

- ✻ Lyme disease is the most common vector-borne disease in the USA
- ✻ The major bacterial diseases transmitted by ticks in the USA are
 - ✻ Lyme disease,
 - ✻ Rocky Mountain spotted fever,
 - ✻ ehrlichiosis,
 - ✻ relapsing fever, and
 - ✻ tularemia.
- ✻ *I. scapularis* ticks transmit three diseases: two bacterial diseases, Lyme disease and human granulocytic ehrlichiosis, and the protozoan disease, babesiosis.

Pathogenesis

- ✱ Pathogenesis is associated with spread of the organism from the bite site through the surrounding skin followed by dissemination via the blood (bacteremia) to various organs, especially the heart, joints, & CNS.
- ✱ No exotoxins, enzymes, or other important virulence factors have been identified.
- ✱ The organism must adapt to two markedly different hosts, the tick & the mammal (either mice or humans.)
- ✱ It does so by changing its outer surface protein (OSP). These OSPs vary antigenically within humans & allow the organism to persist for months to years.

Clinical Findings

- ✱ The clinical findings have been divided into three stages; however, this is a progressive disease, & the stages are not discrete.

✱ Stage 1

- ✱ the most common finding is erythema chronicum migrans (also called erythema migrans), an expanding, erythematous, macular rash that often has a "target" or "bull's eye" appearance.
- ✱ The rash appears between 3 & 30 days after the tick bite. Both the tick bite & the rash are painless & nonpruritic.
- ✱ The rash can, but need not, be accompanied by nonspecific "flu-like" symptoms such as fever, chills, fatigue, & headache.
- ✱ Secondary skin lesions frequently occur.
- ✱ Arthralgias, but not arthritis, are another common finding in the early stage.
- ✱ In approximately 25% of cases of Lyme disease, no rash is seen.



Tick bite rash
erythema migrans
on the thigh
of a child



EM rash on the shoulder



**Pictures of the Lyme disease
bulls eye rash *erythema migrans*.**

Clinical Findings

✿ Stage 2

- ✿ Occurs weeks to months later, cardiac & neurologic involvement predominates.
- ✿ Myocarditis, accompanied by various forms of heart block, occurs.
- ✿ Acute (aseptic) meningitis & cranial neuropathies, such as facial nerve palsy (Bell's palsy), are prominent during this stage.
- ✿ Bilateral facial nerve palsy is highly suggestive of Lyme disease.
- ✿ Peripheral neuropathies also occur.
- ✿ A latent phase lasting weeks to months typically ensues.

Clinical Findings

☀ Stage 3

- ☀ Arthritis, usually of the large joints, e.g., knees, is a characteristic finding.
- ☀ Lyme arthritis is thought to be autoimmune in origin.
- ☀ Chronic progressive CNS disease also occurs.
- ☀ Some patients treated for Lyme infection continue to have prolonged subjective symptoms of fatigue, joint pains, or mental status changes after objective findings have disappeared.
- ☀ No microbiologic evidence for infection has been detected in those patients & prolonged antibiotic therapy has not relieved the symptoms.

Laboratory Diagnosis

- ✿ Cultures are rarely positive & hence are usually not performed.
- ✿ The diagnosis is typically made serologically by detecting either IgM antibody or a rising titer of IgG antibody with an ELISA or an indirect immunofluorescence test.
- ✿ IgM is typically detectable 2 weeks after infection & peaks at 3 to 6 weeks.
- ✿ Serologic tests done before 2 weeks are likely to yield negative results.
- ✿ After 30 days postinfection, tests for IgG are more reliable.

Laboratory Diagnosis

- ✱ Unfortunately, there are problems with the specificity & sensitivity of these tests because of the presence of cross-reacting antibodies against spirochetes in the normal flora.
- ✱ A positive test result should be confirmed with a Western blot analysis.
- ✱ Patients treated early in the disease may not develop detectable antibodies.
- ✱ A PCR (polymerase chain reaction) test that detects the organism's DNA is also available.

Treatment

- ✶ The treatment of choice for stage 1 disease or other mild manifestations is either doxycycline or amoxicillin.
- ✶ For more severe forms or late-stage disease, ceftriaxone is recommended.
- ✶ There is no significant antibiotic resistance.

Prevention

- ✱ Prevention centers on wearing protective clothing & using insect repellents.
- ✱ Examining the skin carefully for ticks is also very important, because the tick must feed for 24 to 48 hours to transmit an infective dose.
- ✱ Should prophylactic antibiotics be given to people who have been bitten by a tick?
- ✱ The decision depends on two main factors: the percentage of infected ticks in the area & the length of time the tick has fed on the person.

Prevention

- ✱ If the percentage of infected ticks is high & the length of time is more than 48 hours, it may be cost-effective to prescribe doxycycline prophylactically.
- ✱ Any person bitten by a tick should be advised to watch carefully for a rash or flulike symptoms for the next 3 weeks.
- ✱ A vaccine containing a recombinant outer surface protein (OspA) of *B. burgdorferi* as the immunogen was available but has been withdrawn.

Leptospira

Leptospira

- ✱ Leptospiras are tightly coiled, fine spirochetes that are not stained with dyes but are seen by darkfield microscopy.
- ✱ They grow in bacteriologic media containing serum.
- ✱ *Leptospira interrogans* is the cause of leptospirosis.
- ✱ It is divided into serogroups that occur in different animals & geographic locations.
- ✱ Each serogroup is subdivided into serovars by the response to agglutination tests.
- ✱ Leptospiras infect various animals including rats & other rodents, domestic livestock, & household pets.

Leptospira

- ✱ In the USA, dogs are the most important reservoir.
- ✱ Animals excrete leptospiras in urine, which contaminates water & soil.
- ✱ Swimming in contaminated water or consuming contaminated food or drink can result in human infection.
- ✱ Outbreaks have occurred among participants in triathlons & adventure tours involving swimming in contaminated waters.
- ✱ Miners, farmers, & people who work in sewers are at high risk.
- ✱ In the USA, the urban poor have a high rate of infection as determined by the presence of antibodies.
- ✱ Person-to-person transmission is rare.

Leptospira

- ✻ Human infection results when leptospiras are ingested or pass through mucous membranes or skin.
- ✻ They circulate in the blood & multiply in various organs, producing fever & dysfunction of the liver (jaundice), kidneys (uremia), lungs (hemorrhage), & CNS (aseptic meningitis).
- ✻ The illness is typically biphasic, with fever, chills, intense headache, & conjunctival suffusion (diffuse reddening of the conjunctivae) appearing early in the disease, followed by a short period of resolution of these symptoms as the organisms are cleared from the blood.
- ✻ The second, "immune," phase is most often characterized by the findings of aseptic meningitis &, in severe cases, liver damage (jaundice) & impaired kidney function.
- ✻ Serovar-specific immunity develops with infection.

Leptospira

- ✧ **Diagnosis** is based on
 - ✧ history of possible exposure,
 - ✧ suggestive clinical signs, and
 - ✧ a marked rise in IgM-anti-body titers.
- ✧ Occasionally, leptospiras are isolated from blood & urine cultures.
- ✧ **The treatment** of choice is penicillin G.
- ✧ There is no significant antibiotic resistance.
- ✧ **Prevention** primarily involves avoiding contact with the contaminated environment.
- ✧ Doxycycline is effective in preventing the disease in exposed persons.

Other Spirochetes

- ✱ Anaerobic saprophytic spirochetes are prominent in the normal flora of the human mouth.
- ✱ Such spirochetes participate in mixed anaerobic infections, infected human bites, stasis ulcers, etc.
- ✱ *Spirillum minor* causes one type of rat bite fever in humans.
- ✱ *Streptobacillus moniliformis*, a gram-negative rod, also causes rat bite fever.

End