

Chapter 29 *Pasteurella*, *Yersinia*, and *Francisella*

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General Concepts

Pasteurella

Clinical Manifestations

In cattle, sheep and birds *Pasteurella* causes a life-threatening pneumonia. *Pasteurella* is non-pathogenic for cats and dogs and is part of their normal nasopharyngeal flora. In humans, *Pasteurella* causes chronic abscesses on the extremities or face following cat or dog bites.

Structure, Classification, and Antigenic Types

Pasteurellae are small, nonmotile, Gram-negative coccobacilli often exhibiting bipolar staining. *Pasteurella multocida* occurs as four capsular types (A, B, D, and E), and 15 somatic antigens can be recognized on cells stripped of capsular polysaccharides by acid or hyaluronidase treatment. *Pasteurella haemolytica* infects cattle and horses.

Pathogenesis

Human abscesses are characterized by extensive edema and fibrosis. Encapsulated organisms resist phagocytosis. Endotoxin contributes to tissue damage.

Host Defenses

Encapsulated bacteria are not phagocytosed by polymorphs unless specific opsonins are present. Acquired resistance is humoral.

Epidemiology

Pasteurella species are primarily pathogens of cattle, sheep, fowl, and rabbits. Humans become infected by handling infected animals.

Diagnosis

Diagnosis depends on clinical appearance, history of animal contact, and results of culture on blood agar. Colonies are small, nonhemolytic, and iridescent. The organisms are identified by biochemical and serologic methods.

Control

Several vaccines are available for animal use, but their effectiveness is controversial. No vaccines are available for human use. Treatment requires drainage of the lesion and prolonged multidrug therapy. *Pasteurella multocida* is susceptible to sulfadiazine, ampicillin, chloramphenicol, and tetracycline.

Yersinia

Clinical Manifestations

Yersinia pestis causes bubonic and pneumonic plague. Bubonic plague is transmitted by the bite of infected rat fleas. Swollen, blackened lymph nodes (buboes) develop, followed by septicemia and hemorrhagic pneumonia and death. The pneumonic form spreads directly from human to human via respiratory droplets. Outbreaks are explosive in nature, and invariably lethal. *Yersinia enterocolitica* causes severe diarrhea and local abscesses, and *Y pseudotuberculosis* causes severe enterocolitis.

Structure, Classification, and Antigenic Types

Yersinia are small, Gram-negative coccobacilli showing bipolar staining. The capsular or envelope antigen is heat labile. Somatic antigens V and W are associated with virulence.

Pathogenesis

In bubonic plague, the bacilli spread from a local abscess at the flea bite site to draining lymph nodes; followed rapidly by septicemia and hemorrhagic pneumonia. *Yersinia enterocolitica* enters via the Peyer's patches following ingestion of contaminated water or food and cause severe liver and splenic abscesses. *Yersinia pseudotuberculosis* causes enlarged, caseous nodules in the Peyer's patches and mesenteric lymph nodes.

Host Defenses

Specific anti-envelope antibodies are opsonic and protective. Cell-mediated resistance may also be involved.

Epidemiology

Yersinia pestis is primarily a rat pathogen. Human infections are initially transmitted by rat fleas, but later the disease may shift into the pneumonic form and continue by direct person- to-person spread. *Yersinia enterocolitica*, a pathogen of deer and cattle spreads to humans via contaminated drinking water.

Diagnosis

Early clinical diagnosis is essential in plague. Blood cultures are positive for *Y pestis*. Sputum may show large numbers of small bacilli when stained with fluorescent antibody. *Yersinia pestis* is an extremely infectious hazard for nursing and laboratory personnel.

Control

Control of rats and rat fleas is crucial. Laboratory personnel should be vaccinated. *Yersinia pestis* is susceptible to sulfadiazine, streptomycin, tetracycline, and chloramphenicol. *Yersinia enterocolitica* is best controlled by purifying drinking water and pasteurizing dairy products. *Yersinia pseudotuberculosis* disease requires aggressive treatment with ampicillin and tetracycline.

Francisella

Clinical Manifestations

Francisella tularensis causes *tularemia*, with high fever, acute septicemia and toxemia. Oral infection causes typhoid-like disease.

Structure, Classification, and Antigenic Types

The organisms are small, nonmotile, Gram-negative coccobacilli. *Francisella* is nutritionally demanding. It is biochemically similar to the brucellae, but antigenically distinct.

Pathogenesis

A local abscess at the site of infection is followed by septicemia with rapid spread to the liver and spleen; 30 percent of untreated patients die.

Host Defenses

Cell-mediated immunity is protective and long lasting.

Epidemiology

Francisella is primarily a pathogen of squirrels and rabbits; humans are infected by the bite of an infected deerfly or tick or by handling infected rabbit carcasses or eating undercooked meat.

Diagnosis

Cultivation from blood or biopsy material is difficult and slow. Blood smears can be stained with specific fluorescent antibody. Hemagglutinins appear in 10 to 12 days; a rising titer is diagnostic.

Control

A live attenuated vaccine is available for laboratory personnel. Goggles should be worn in the laboratory to prevent conjunctival infection. *Francisella* is susceptible to streptomycin, tetracycline, and chloramphenicol.

Introduction

The genus *Pasteurella* was originally proposed and described by Trevisan in 1887. It consisted of a group of nonmotile, small (0.7 μm by 0.5 μm), Gram-negative coccobacilli often exhibiting a characteristic type of bipolar staining (Fig. 29-1). Most members of this genus are associated with severe, life-threatening systemic diseases involving both hemorrhagic pneumonia and septicemia. The first pathogen to be studied (called at that time *Pasteurella septica*) was shown to be responsible for hemorrhagic septicemia in cattle and sheep, and fowl cholera in chickens. This organism, used by Pasteur for his milestone vaccination studies in 1880, is now called *Pasteurella multocida*. Adult animals may carry this organism as part of their normal nasopharyngeal or gingival microflora and may infect young, susceptible animals which develop a fulminating, rapidly lethal hemorrhagic pneumonia. The incubation period for this disease may be as short as 12 hours with very high mortality rates (80 to 100 percent). The disease can spread explosively through an apparently normal herd or flock.

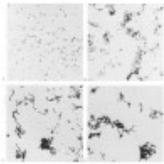


Figure 29-1

(A) *Pasteurella multocida* growth on brain-heart infusion agar. (B) *Francisella tularensis* growth on chocolate blood agar. (C) *Yersinia pestis* growth on tryptosis soy agar. (D) *Yersinia enterocolitica* growth on tryptose soy agar. (Gram stain, X1,200.) (more...)

Two other important pathogens were initially included in this genus. The first was *Pasteurella pestis* (the plague bacillus), which was isolated and described almost simultaneously by Kitasato and by Yersin in 1894. This organism is primarily a pathogen of the rat (one of a select group of acute bacterial pathogens for this host). For taxonomic reasons, it was decided in 1971 to place the plague bacillus in a new genus as *Yersinia pestis*, together with *Y pseudotuberculosis* and *Y enterocolitica*. The latter infect a variety of rodent species but can cause severe intestinal disease in humans. Finally, a third genus was created for an organism originally grouped with *P pestis*, but now known as *Francisella tularensis*, the agent of tularemia in rodents and humans. The various diseases caused by these three genera, together with the vectors responsible for their spread to humans, are summarized in [Table 29-1](#).

Organism	Disease	Vector	Host
<i>Pasteurella multocida</i>	Septicemia, abscesses	Cats, dogs	Cattle, humans, birds
<i>Yersinia pestis</i>	Plague	Flies, fleas	Rats, humans
<i>Yersinia pseudotuberculosis</i>	Septicemia, abscesses	Flies, fleas	Rats, humans, birds
<i>Yersinia enterocolitica</i>	Septicemia, abscesses	Flies, fleas	Rats, humans, birds
<i>Francisella tularensis</i>	Tularemia	Flies, fleas	Rats, humans, birds

Table 29-1

Disease and Vector Comparisons for *Pasteurella*, *Yersinia*, and *Francisella*.

Metabolically, these organisms are facultative anaerobes which grow best on nutrient media enriched with blood, hematin, or catalase. Most members show a restricted fermentative capacity. Although they grow well when incubated at 37°C, they can also multiply at room temperature, when some species produce putative virulence factors that help to establish the pathogen within the tissues. Vaccines are of limited value and aggressive treatment with broad-spectrum antibiotics is required to control human infections.

Pasteurella

Clinical Manifestations

Although *P multocida* is an awesome pathogen for young cattle and birds, it may occur as a relatively benign member of the nasopharyngeal microflora of adult cattle, rabbits, cats, and dogs which do not usually develop severe pulmonary infections. Humans do not usually develop acute pulmonary disease, although there have been reports of a mild pasteurellosis in some cattle handlers. It seems likely that this organism can colonize normal human nasopharyngeal membranes.

Most human infections with *P multocida* occur as localized abscesses of the extremities or face as a result of cat or dog bites (Fig. 29-2). Historically, such infections were first associated with tiger bites in India. Domestic cats, as well as exotic felines, carry *P multocida* as part of their normal gingival microflora; organisms introduced into human tissues as a result of bites and scratches enter the subcutaneous tissues, quickly producing severe local abscesses, which eventually spread to the draining lymph nodes (Fig. 29-2). These abscesses require surgical drainage due to their extensive edema and fibrosis (which also reduces the effectiveness of chemotherapeutic intervention, although this organism is susceptible to most antibiotics in vitro).

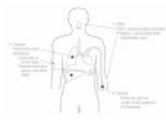


Figure 29-2

Pathogenesis of *P. multocida*.

Adult cattle may carry virulent strains of *P. multocida* as part of their normal nasopharyngeal flora with no obvious sign of infection until they are stressed by dehydration, poor nutrition, overcrowding, or an intercurrent viral infection. The dynamics of the resulting pulmonary infection are complex, and the controlling factors are still poorly understood. Young animals are infected by older carriers shortly after birth, while still immunologically immature, and develop an acute pneumonia and septicemia, especially when herded into crowded transports or feedlots (hence the name shipping fever). Death can occur 12 to 18 hours after the onset of symptoms. Similarly, chicken and turkey flocks can be decimated by an overwhelming pneumonia that sweeps through a previously healthy flock, apparently as a result of waterborne spread from a single infected carrier.

Rabbits are highly susceptible to chronic nasopharyngeal infections caused by *P. multocida*, developing a characteristic “snuffles”, often associated with a purulent otitis media. This infection may progress to a life-threatening hemorrhagic pneumonia when the animal is stressed as a result of the hyperimmunization procedures used during antibody production. Attempts to develop pasteurilla-free rabbit breeding stocks have had only limited success.

Mice are extraordinarily susceptible to parenteral and aerogenic challenge with *P. multocida*, especially by strains obtained from cattle and fowl sources. Introduction of fewer than 10 viable *P. multocida* serotype A organisms into the lungs of a normal mouse is followed by logarithmic growth in which the systemic disease overwhelms the host defenses in a matter of hours. The virulent encapsulated organism resists phagocytosis and multiplies freely within the extracellular spaces and fluids of the lung (Fig. 29-3). The host dies with no sign of any humoral or cellular immune response. In fact, the rate of growth by the pathogen in vivo is little different from that observed in laboratory media. Large numbers of viable bacilli appear within the bloodstream in a matter of hours and can be recovered from virtually every organ of the moribund host. Curiously, the same organism shows little ability to cross the intact intestinal mucosa, and large numbers of viable bacilli can be introduced intragastrically with no harm to the host, provided that appropriate precautions are taken to prevent accidental inoculation into the lung.



Figure 29-3

Protection against *P. multocida* is mediated by opsonic antibodies.

Pasteurella hemolytica causes a life-threatening hemorrhagic pneumonia in horses and cattle, but does not appear to infect humans.

Structure, Classification, and Antigenic Types

Pasteurella multocida is a small, nonmotile Gram-negative coccobacillus, which often exhibits bipolar staining, in which the ends of the bacilli stain more intensely than the middle. These bacteria possess both capsular and somatic antigens, and isolates can be divided into four distinct capsular types (A, B, D, and E) on the basis of an indirect hemagglutination test. As many as 15 somatic antigens can be recognized once the capsular layer has been removed by acid or hyaluronidase treatment. Most fowl and human isolates are type A, whereas most cattle strains are type B. Type E strains are associated mostly with bovine hemorrhagic septicemia in central

Africa. Freshly isolated strains may produce large mucoid colonies rich in hyaluronic acid. However, after several transfers on solid media, most virulent strains produce smooth, translucent colonies that become rough (untypable) following prolonged cultivation on laboratory media.

Pathogenesis

Pasteurella species are primarily pathogens of cattle, sheep, fowl, and rabbits. Humans may become infected while handling infected animals. Human abscesses are characterized by extensive edema and fibrosis. Encapsulated organisms resist phagocytosis. Endotoxin contributes to tissue damage.

Host Defenses

Pasteurella multocida is an extracellular parasite that multiplies freely at the site of implantation despite the influx of polymorphonuclear leukocytes (PMNs) into the lesion. In the absence of specific opsonins (immune antibodies), the organisms are not phagocytosed but multiply rapidly within the tissue fluids. Acquired resistance to pasteurellosis is humorally mediated and protection can be passively transferred to naive recipients by means of hyperimmune serum but not by spleen cells harvested from the same donor. Once opsonized, the Pasteurellae are rapidly phagocytosed and inactivated, so that the number of viable bacilli within the lesion declines sharply instead of multiplying. More importantly, hematogenous spread (a feature of the normal infection pattern) is completely ablated by specific antibodies, preventing the establishment of a fatal pneumonia. This protective effect occurs long before any mononuclear cell response has time to develop. Killed whole-cell vaccines (bacterins) induce a substantial B-cell response, leading to copious plasma cell production and the release of specific anticapsular antibodies into the bloodstream (Fig. 29-3). These opsonins can passively transfer high levels of specific antibacterial immunity to naive recipients, at least in the laboratory. The situation is more complicated in practice. Field trials with a number of multivalent *P multocida* vaccines containing adjuvant have yielded generally disappointing and inconsistent results, possibly owing to the large number of different serotypes present in the environment of the test population under most field test conditions. Recently, several live attenuated vaccines (usually presented in drinking water) have been claimed to be effective against fowl cholera outbreaks in turkey flocks.

Diagnosis

Pasteurella multocida grows readily on nutrient blood agar to produce small, nonhemolytic, iridescent colonies. Highly mucoid colonies are occasionally seen on primary isolation. There is no growth on MacConkey agar, and most strains ferment only glucose and sucrose, with no gas production.

Control

Pasteurella multocida is susceptible to sulfadiazine, ampicillin, chloramphenicol, and tetracycline in vitro. Because of the acute nature of most animal infections, chemotherapy is of limited value. In human cases, localized abscesses resolve quite slowly and may require prolonged therapy with multiple antibiotics. The organism is susceptible to mild heat (55°C), as well as to exposure to most hospital disinfectants. Organisms in dried blood may remain viable at room temperature for several weeks. Vaccines are not available for human use.

Yersinia

The genus *Yersinia* contains three species of medical importance: *Y. pestis*, the agent of bubonic and pneumonic plague, and *Y. pseudotuberculosis* and *Y. enterocolitica*, both of which can result in severe gastroenteritis, with local abscess formation and death as a result of peritonitis.

Clinical Manifestations

Yersinia pestis is primarily a rodent pathogen, with humans being an accidental host when bitten by an infected rat flea (Fig. 29-4). The flea draws viable *Y. pestis* organisms into its intestinal tract with its blood meal. These organisms multiply in situ sufficiently to block the proventriculus, and some organisms are regurgitated into the next bite wound, transferring the infection to a new host. While growing in the invertebrate host, *Y. pestis* loses its capsular layer, and most of the organisms are phagocytosed and killed by the polymorphonuclear leukocytes which enter the infection site in large numbers. However, a few bacilli are taken up by tissue macrophages, which are unable to kill them but provide a protected environment for the organisms to resynthesize their capsular and other virulence antigens. The re-encapsulated organisms kill the macrophage and are released into the extracellular environment, where they resist phagocytosis by the polymorphs. The resulting infection quickly spreads to the draining lymph nodes, which become hot, swollen, tender, and hemorrhagic, giving rise to the characteristic black buboes responsible for the name of this disease (Fig. 29-4). Within hours of the initial flea bite, the infection spills out into the bloodstream, leading to substantial involvement of the liver, spleen, and lungs. As a result, the patient develops a severe bacterial pneumonia, exhaling large numbers of viable organisms into the air during coughing fits. Up to 90 percent of untreated patients will die representing a highly contagious health hazard to nursing staff. As the epidemic of bubonic plague develops (especially under conditions of severe overcrowding, malnutrition, and heavy ectoparasite infestation), it eventually shifts into a predominately pneumonic form (Fig. 29-4), which is far more difficult to control and which has 100 percent mortality. Experimentally, a conjunctival infection route has been demonstrated in monkeys and guinea pigs, and it is likely that many laboratory-derived infections occur via this route.

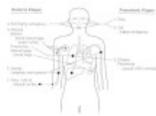


Figure 29-4

Pathogenesis of *Y. pestis* in plague patients.

Structure, Classification, and Antigenic Types

Yersinia pestis is a small, Gram-negative coccobacillus, which frequently shows strong bipolar staining. However, pleomorphic and club-shaped forms are not unusual. Freshly isolated cultures often exhibit substantial slime production, due to a so-called capsular or envelope antigen which is heat labile and is readily lost when the organism is growing in vitro or in the insect vector (Table 29-2). Fully virulent strains possess V and W (virulence) antigens, which are highly toxic for the mouse and, to a lesser extent, for guinea pigs (Table 29-2).

TABLE 29-2 Antigenic Makeup of <i>Y. pestis</i>	
Antigen	Location
V	Virulence
W	Virulence
Y	Yersinia
Y ₁	Yersinia
Y ₂	Yersinia
Y ₃	Yersinia
Y ₄	Yersinia
Y ₅	Yersinia
Y ₆	Yersinia
Y ₇	Yersinia
Y ₈	Yersinia
Y ₉	Yersinia
Y ₁₀	Yersinia
Y ₁₁	Yersinia
Y ₁₂	Yersinia
Y ₁₃	Yersinia
Y ₁₄	Yersinia
Y ₁₅	Yersinia
Y ₁₆	Yersinia
Y ₁₇	Yersinia
Y ₁₈	Yersinia
Y ₁₉	Yersinia
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Y ₂₂	Yersinia
Y ₂₃	Yersinia
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Y ₂₅	Yersinia
Y ₂₆	Yersinia
Y ₂₇	Yersinia
Y ₂₈	Yersinia
Y ₂₉	Yersinia
Y ₃₀	Yersinia
Y ₃₁	Yersinia
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Y ₉₇	Yersinia
Y ₉₈	Yersinia
Y ₉₉	Yersinia
Y ₁₀₀	Yersinia

Table 29-2

Antigenic Makeup of *Y. pestis*.

Pathogenesis

The virulence of *Y pestis* strains can be equated to the rate of growth (or elimination) of the organisms in the spleen following intravenous inoculation (Fig. 29-5). The most virulent strains multiply logarithmically with no initial lag phase, reaching lethal proportions within 2 or 3 days. Infected animals exhibit a progressive septicemia and die as a result of a hemorrhagic pneumonia. Less virulent strains begin to multiply in vivo only after an initial lag period and this slowed early growth allows the host defenses time to mount an effective immune response (Fig. 29-5).

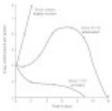


Figure 29-5

Growth of *Y pestis* in intravenously infected mice showing combined viable counts for spleen and liver homogenates. The virulence of *Y pestis* correlates with rate of growth in the mouse. The highly virulent Shasta strain killed 100 percent of infected (more...)

Host Defenses

The major defense against *Y pestis* infection is the development of specific anti-envelope (F1) antibodies, which serve as opsonins for the virulent organisms, allowing their rapid phagocytosis and destruction while still within the initial infectious locus (Fig. 29-6). Although the V and W antigens are associated with virulence, a number of avirulent strains may also possess them, and some individuals possessing high anti-VW antibody titers will nevertheless undergo a second attack of this disease. Therefore, the immune mechanism(s) against this disease is extremely complex and involves a combination of humoral and cellular factors. The convalescent host is solidly immune (at least for a time) to virulent rechallenge, the inoculum being eliminated as though the organisms were completely avirulent. Killed *Y pestis* vaccines (especially when given with a suitable adjuvant) induce some measure of host protection, although this will be less effective than that afforded by the live infection.

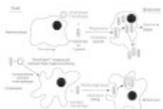


Figure 29-6

Protection against *F tularensis* or *Y pestis* is cell-mediated.

Epidemiology

Bubonic plague — the Black Death — one of the great epidemic scourges of mankind, swept across Europe and Asia in a series of devastating pandemics during the Middle Ages. This disease may have been responsible for the death of one-third of the world's population at that time. Then, for largely unknown reasons, bubonic plague suddenly ceased to be an important pandemic disease, and no major epidemics have occurred in Europe or North America in more than a century. Sporadic outbreaks of sylvatic plague still occur in wild rats, squirrels and prairie dogs in the western United States, and endemic plague has been reported in parts of Southeast Asia. Although no recent deaths due to plague have been reported in the United States, occasional isolates of *Y pestis* appear to be fully virulent for experimental animals. The striking change in the epidemiology of this disease is probably due to such nonspecific factors as improved rodent control and the widespread use of insecticides against the insect vector. Recent advances in our understanding of the molecular biology of microbial virulence factors associated

with this pathogen offer the promise of improved subunit immunogens capable of inducing a fully effective acquired resistance.

Diagnosis

Yersinia infections must be diagnosed quickly due to the extraordinary virulence of these organisms. Death from pneumonic plague can occur in as little as 24 hours after the first appearance of clinical symptoms. Sputum specimens from these patients contain large numbers of Gram-negative coccobacilli. Blood cultures are positive, and lymph node biopsy material shows a massive inflammatory cell infiltrate, together with numerous cell-free coccobacilli. The organisms can be identified using a fluorescent antibody staining technique, and the epidemiology of the outbreak can be traced by bacteriophage typing.

Yersinia pestis poses a serious infectious hazard for nursing and laboratory personnel. Protective clothing and a full face respirator should always be worn when working with this organism. Cultivation and virulence testing of this organism should be attempted only in P-3 containment facilities by staff who have been immunized recently with live attenuated vaccine. Animals should be checked to ensure that they are free of ectoparasites.

Control

Yersinia can be killed by mild heat (55°C) and by treatment with 0.5 percent phenol for 15 minutes. It is susceptible to sulfadiazine, streptomycin, tetracycline, and chloramphenicol in vitro. Thus far, few drug-resistant strains have emerged. Control measures against plague center largely on rat flea eradication programs, which have been credited with preventing epidemics of plague in Europe in 1945 and in Southeast Asia during the Vietnam war. Attempts to eradicate the rodent reservoir have been unsuccessful, and it seems unlikely that rat plague will ever be completely eliminated world-wide.

Yersinia Pseudotuberculosis

Yersinia pseudotuberculosis is a natural pathogen of rodents and birds but can infect humans, causing a severe enterocolitis with enlarged caseous nodules in the Peyer's patches and the mesenteric lymph nodes. These lesions often resemble those seen during intestinal tuberculosis. The organism is highly infectious for guinea pigs and can result in devastating outbreaks of pseudotuberculosis in breeding colonies, with very high mortality rates. This infection is virtually impossible to eliminate once established. *Yersinia pseudotuberculosis* can be readily distinguished from other *Yersinia* species because of its motility when grown at 25°C.

In humans, *Y pseudotuberculosis* causes severe intestinal abscesses that require aggressive chemotherapy with ampicillin and tetracycline. No vaccine is available.

Yersinia enterocolitica

Yersinia enterocolitica is a natural pathogen of cattle, deer, pigs, and birds. Most infected animals recover from their primary disease, remaining healthy carriers indefinitely. The organism is excreted in large numbers in the feces by infected carriers and can contaminate drinking water and dairy products. Oral infection results in a severe diarrhea in humans, together with necrosis of the Peyer's patches, chronic lymphadenopathy, and hepatic and splenic abscesses (Fig. 29-7). An increasing number of human outbreaks have been reported in recent years, mostly in colder climates. This may reflect a greater awareness of the disease, (together

with improved isolation and diagnostic procedures) rather than an actual increase in the overall incidence of this disease in humans.

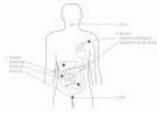


Figure 29-7

Pathogenesis of *Y. enterocolitica*.

Most *Y. enterocolitica* isolates are avirulent for laboratory rodents. Recently, several mouse virulent strains have been isolated from human pathologic material. Orally infected mice develop progressive involvement of the ileal Peyer's patches, with abscess formation in the mesenteric lymph nodes, liver, and spleen. Eventually, most of the animals die when these intestinal abscesses undergo perforation and peritonitis. The lesions typically contain large numbers of PMNs but there is also a strong mononuclear cell response, which may be important to the successful control of this infection.

The best prevention methods for *Y. enterocolitica* infections are adequate water purification and milk pasteurization. Once the infection becomes established within the gut-associated lymphoid tissues, it produces chronic abscesses, which require aggressive chemotherapy involving a combination of ampicillin, chloramphenicol, and polymyxin. No vaccine is available for this infection.

Francisella

Clinical Manifestations

Francisella tularensis causes tularemia, which is spread naturally to humans directly by ticks and deerflies (Fig. 29-8). Most strains that infect rabbits are highly infectious and virulent for humans. The subcutaneous infectious dose may be as low as 10 viable bacilli, with a mortality as high as 30 percent in untreated patients. Infections may result from local trauma incurred while skinning and dressing infected rabbit carcasses. Hence, protective gloves and goggles should always be worn while performing this chore in an endemic area. Humans can also contract the disease by eating inadequately cooked, infected rabbit meat. The resulting tularemia is a severe typhoidlike intestinal disease, with local abscess formation in the Peyer's patches and the mesenteric lymph nodes (Fig. 29-7). It is associated with high fever and a severe toxemia (septicemia). *Francisella tularensis* is a facultative intracellular parasite, which induces a strong mononuclear cell immune response on the part of the host defenses (Fig. 29-3). A humoral response also develops, although the precise nature of the relationship between the specific antibodies and resistance to the naturally acquired disease is still not altogether clear. Actively infected mice develop a strong, delayed-type skin hypersensitivity to sensitins produced by this organism.

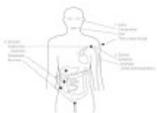


Figure 29-8

Pathogenesis of *F. tularensis*.

Laboratory infections may occur via the conjunctival route; this probably explains the high infection rate seen in laboratory personnel working with this pathogen. Goggles and a face mask should always be worn when working with virulent strains of this organism. Staff should be immunized with the live attenuated vaccine. Animal infection studies must be performed under

P-3 containment conditions, and, whenever possible, experimental studies should use the vaccine strain.

Structure, Classification, and Antigenic Types

Francisella tularensis is a nonmotile, Gram-negative coccobacillus, which forms small translucent colonies on glucose blood agar or on Dorset egg slants. The organism grows readily in developing chicken embryos. Nutritionally and biochemically it bears a close resemblance to the Brucellae, but it can be differentiated from members of this genus on the basis of DNA homology tests. It is a natural pathogen of rodents (squirrels and rabbits mainly), but can be carried by birds, which usually develop latent infections.

Pathogenesis

Mice, rats, guinea pigs, and rabbits are readily infected with *F tularensis* via the subcutaneous, nasal, or conjunctival routes. Virulent strains multiply logarithmically within the liver and spleen (but not the lungs), and death usually occurs 5 to 8 days later. In sublethally challenged animals, the systemic infection peaks and declines rapidly, a response associated with cell-mediated immunity, which can be transferred adoptively to naive recipients by splenic immune T cells, but not by hyperimmune serum. Most clinical isolates lose virulence when maintained for long periods on laboratory media and eventually cannot produce progressive disease in susceptible animals.

Host Defenses

Acquired resistance following recovery from tularemia is cellular, long lasting and highly protective.

Diagnosis

Isolation of *F tularensis* from pathologic material can be difficult and slow. Best growth occurs on cysteine-glucose-blood agar, but plates should be incubated at 37°C for at least 3 weeks before being discarded as negative. Smears of pathologic material or blood cultures may be stained using fluorescent antibodies directed against specific surface antigens of the organism. Hemagglutinins appear in serum samples some 10 to 12 days after infection and slowly increase in titer for up to 8 weeks. A rising titer is always diagnostic of active disease.

Control

Francisella tularensis is susceptible to inactivation by mild heat (55°C for 10 minutes) and disinfectants. It is susceptible to streptomycin, tetracycline, and chloramphenicol in vitro. Relapses are not uncommon if treatment is stopped before all the viable bacilli have been eliminated from the tissues. Infection control measures usually entail the elimination of the insect vectors.

Killed *F tularensis* vaccines are not very effective, even when presented in adjuvant. A live attenuated vaccine has been developed and should be used to immunize laboratory staff working with this organism.

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