Zoonoses

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9

INFECTIOUS DISEASES IN HUMANS AND OTHER ANIMALS: FROM "US VERSUS THEM" TO "SHARED RISK"

The history of contact between animals and humans has always involved infectious diseases, and today more than half of the infectious diseases of humans are zoonotic in origin. In fact, the majority of "emerging" infectious diseases in the past three decades are zoonotic. Therefore the control and prevention of these diseases can be accomplished only through improving approaches to reducing disease transmission among humans and other animals.

Despite the great deal of attention that has been focused on emerging infectious zoonotic diseases, including severe acute respiratory syndrome (SARS), West Nile virus, monkeypox, and avian influenza, there has been less discussion and effort targeted at the environmental "drivers" of such diseases. One possible reason is that the traditional approach of the human health community to zoonotic disease has been an "us versus them" approach. The problem is viewed as an infectious animal reservoir that then poses an infectious risk to humans—either through direct contact with infected animals and their excretions, meat, milk, or other tissues, or via a vector transmission bringing the pathogen from the animal population into human hosts. The control of such "us versus them" diseases has traditionally involved measures such as control of the animal reservoir (through culling, quarantine, or vaccination) or vector control (through pesticides and personal protection). For many zoonotic diseases, however, such approaches are limited because the ultimate causes of infection in the animals may not be addressed sufficiently. For example, Nipah virus emerged as a deadly pathogen in Malaysia when pig farms were built close to forest areas frequented by fruit bats (Figure 9-1 and Color Plate 9-1). These fruit bats, natural

Figure 9-1 ■ Collection of oral swab from anesthetized spectacled flying fox *(Pteropus conspicillatus)* for Hendra virus antigen detection. (From Fowler ME, Miller RE: *Zoo and wild animal medicine: current therapy*, ed 6, St Louis, 2008, Saunders Elsevier. Courtesy Jack Shield.)

hosts for Nipah and other henipaviruses, had sufficient contact with the pig farms to allow the virus pathogen to "spill over" from the wildlife reservoir into the domestic pig population, causing mortality for pigs and humans (and cats) in contact with them.[1]

Therefore, for many infectious diseases that cross between animals and humans, it is advisable for human health professionals to move beyond an "us versus them" view of animals and infections and to instead join veterinarians and public health professionals to examine the environmental forces driving disease emergence that constitute a "shared risk" of infection for both humans and animals.[2] Figure 9-2 outlines these relationships.

This chapter presents this shared risk approach for a number of zoonotic diseases. For each disease, environmental risk factors (drivers) of infectious risk are discussed, as well as practical steps that public health, human health, and animal health professionals can take to prevent, control, diagnose, and treat such infections. A key step with each disease is providing accurate information about risk to clients and other members of the health professions.

NON-ZOONOSES (FOR NOW)

Infection in animals can be a warning signal of infectious disease risk to humans, and sometimes the converse is true. At the same time, many animal diseases currently are not believed to pose a threat to humans, and many human infectious diseases do not appear to infect pets and other animals.

Experience has shown that this situation may change as organisms continue to adapt to new environments and acquire mutations that allow them to cross species barriers. Nonetheless, human health clinicians should (1) be aware of animal diseases that, based on current knowledge, do not appear to cause disease in humans and (2) be able to reassure patients who express such concerns. Similarly, clinicians can correct

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Figure 9-2 ■ Relation between environmental drivers of infectious disease and health outcomes in humans and animals. (From Rabinowitz PM, Odofin L, Dein FJ: From "us vs. them" to "shared risk": can animals help link environmental factors to human health? *Ecohealth* 5(2):224, 2008.)

Table 9-1 ■ Common Infectious Diseases of Companion Animals Not Currently Believed to Be Zoonotic			
Disease	**Agent**	**Species Affected**	**Signs/Comment**
Feline immunodeficiency virus infection (feline AIDS)	Feline immunodeficiency virus: retrovirus in the same genus as HIV, the causative agent of AIDS in humans[3]	Cats	Infected cats are at risk of opportunistic infections. FIV is used as a research model for HIV.
Canine parvovirus infection	Canine parvovirus 2 (CPV-2), DNA virus	Dogs (especially puppies)	Cause of acute debilitating diarrhea and death in untreated young dogs. Related to feline panleukopenia virus causing "feline distemper." In humans, a different strain of parvovirus (parvovirus B19) causes fever and rash (fifth disease) in children and serious infection in pregnancy.
Canine distemper	Canine distemper virus (CDV): Morbillivirus (Paramyxovirus family), related to measles virus	Dogs and other carnivores, including ferrets, raccoons, skunks, foxes, large felines, seals	Febrile disease, often fatal neurological involvement; respiratory signs can occur. Humans may become subclinically infected.[3] "Feline distemper" of domestic cats is a panleukopenia virus, similar to canine parvovirus.
Feline leukemia virus infection	Feline leukemia virus (FeLV)	Cats	Used as natural model for human cancer; zoonotic potential is controversial.

misinformation regarding species-specific human diseases that patients may believe come from animal contact. For example, human pinworm infection is not a zoonotic disease. Table 9-1 lists some of these non-zoonoses. As this list shows, many of these agents, while currently not considered zoonotic to any significant degree, bear some relation to human pathogens.

DISEASES TO WATCH

The sections in this chapter present individual descriptions of zoonotic diseases that human health and veterinary clinicians and public health professionals in the United States may encounter in their clinical work. It has been estimated, however, that there are more than 1600 known zoonotic pathogens, some of which are considered to be "emerging" in terms of expanding their geographical range or pathogenicity to other species. Our knowledge of the zoonotic potential of many infectious pathogens is continually changing as new evidence, some based on improved techniques of molecular diagnosis, appears.

Table 9-2 presents a number of pathogens and diseases for which clinicians and public health professionals should

maintain an awareness of possibly increasing zoonotic disease risk. Table 9-3 lists a number of currently recognized zoonotic pathogens and some of the species for which the pathogen has been reported.

References

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Table 9-2 ▪ Diseases and Agents "to Watch" in Terms of Zoonotic Potential

Disease	Agent	Animal Hosts	Zoonotic Transmission Route	Clinical Manifestations	Comments
Bordetella	*Bordetella bronchiseptica* bacteria	Dogs, rabbits, guinea pigs	Respiratory	Cough, fever; disease seen mostly in immune-compromised humans	A cause of "kennel cough" in dogs
Chagas disease	*Trypanosoma cruzi* protozoa	Rodents rabbits, opossums, dogs, cats, armadillos	Organism in feces of *Triatoma* bug ("kissing" bug or "assassin" bug) can enter wound; blood transfusion	Fever, myocarditis, hepatosplenomegaly	Dogs exhibit clinical signs similar to those in humans Other animals are carriers; dogs infected in southern United States; dogs may be extending the range of this disease
Chikungunya	Chikungunya virus	Humans, rodents, birds, primates	*Aedes* mosquito vector (present in United States)	Fever, rash, arthralgia	Seen in returning travelers, new cases in Europe
Dirofilariasis ("heartworm" in dogs)	*Dirofilaria immitis* roundworm	Dogs, cats, ferrets, raccoons, bears	Mosquito vector	Fever, cough, "coin lesion" in lung due to vasculitis, reported involvement of extrapulmonary sites (CNS, liver)[4]	Parasite not known to complete its life cycle in humans
Erysipeloid (human disease)	*Erysipelothrix rhusiopathiae* bacteria	Pigs, sheep, turkeys, pigeons, marine mammals, fish	Direct contact	Cellulitis	Occupational disease of farmers, butchers, cooks
Feline cowpox	Feline cowpox virus	Cats are principal host; rodents, cows, and humans are accidental hosts	Direct contact	Skin ulcer resembling anthrax	Distribution is Eurasia
Pseudomembranous colitis	*Clostridium difficile* bacteria	Cattle	Ubiquitous organism; may preset with overuse of antibiotics	Diarrhea, abdominal pain	Emerging community-acquired infection Strains in humans recently found to match those in cattle
Glanders	*Burkholderia mallei* bacteria	Horses, mules, donkeys	Direct contact	Four forms of disease: septicemia, pulmonary infection, local infection, chronic infection	Category B bioterrorism agent

Helicobacter infection	*Helicobacter:* gram-negative bacteria: *H. pylori* (humans), *H. felis* (cats), *H. canis* (dogs)[3]	Dogs, cats, birds	Ingestion	Peptic ulcer disease, gastritis, gastric neoplasia in humans	
Monkeypox	Monkeypox virus	African rodents (able to infect prairie dogs, rats, mice, squirrels), primates, rabbits	Bites, aerosols, direct contact	Flulike symptoms, rash	Caused outbreak in humans and pet prairie dogs related to importation of Gambian rats and other African rodents intended as exotic pets
Melioidosis (pseudoglanders)	*Pseudomonas pseudomallei* bacteria	Rodents, goats, sheep, horses, swine, primates, dogs, birds, dolphins, tropical fish	Acquired from the environment	Infection of skin, lung, hepatitis	Category B bioterrorism agent, occurs in zoo animals[5]
Pasteurellosis	*Pasteurella multocida* bacteria	Dogs, cats, other animals	Scratch, bite, but also secretions	Wound infection, but UTI recently reported[6]	
Rat-bite fever (Haverhill fever)	*Streptobacillus moniliformis* bacteria	Rodents, including laboratory and wild animals	Bites and scratches, ingestion	Uncommon; risk to laboratory animal workers	
Streptococcosis	*Streptococcus suis* (and other species) bacteria	Pigs	Direct contact, aerosols, fomites	Fever, endocarditis	35 serotypes; type 2 is most frequently isolated from pigs with clinical signs and from humans[7]; occupational disease of pig handlers
Yersiniosis	*Yersinia enterocolitica* bacteria	Pigs	Ingestion, especially of undercooked pork	Diarrhea, abdominal pain	

CNS, Central nervous system; *UTI*, urinary tract infection.

Table 9-3 ■ Chart of Species and Associated Pathogens

Disease	Domestic																														
	Dogs	Cats	Ferret	Reptiles and amphibians	Caged birds	Rabbits	Pocket pets (rodents)	Fish	Horses	Cattle	Goats	Sheep	Swine	Poultry	Mink	Nonhuman primates	Camels, llamas, alpacas	Raccoons	Squirrels	Other wild rodents	Wild birds	Marine mammals	Wild cats	Foxes, coyotes, wild canids	Bats	Skunks	Opossums	Elephants	Beavers	Deer	Other wild herbivores
Arthropods																															
Scabies	X	X	X				X			X	X	X	X				X														
Other acariasis	X	X	X	X	X	X									X				X	X			X		X	X				X	
Bacterial																															
Anthrax	X	X								X	X	X	X	X			X													X	X
Bartonellosis		X																							X						
Bordetella bronchiseptica	X					X	X																								
Botulism	X								X	X	X		X	X	X						X										
Brucellosis	X						X			X	X	X	X	X	X		X			X				X						X	X
Campylobacteriosis	X	X	X	X	X		X			X	X	X	X	X	X	X				X											
Chlamydophila infection	X		X		X	X	X			X	X	X	X			X				X										X	
Ehrlichiosis and anaplasmosis	X	X								X	X	X	X				X	X		X	X			X						X	X
Escherichia coli O157 infection	X									X	X	X		X																X	
Erysipeloid								X														X									
Leptospirosis	X	X				X	X		X	X	X	X	X					X	X	X			X				X			X	
Lyme disease	X	X				X	X		X	X									X	X							X			X	
Melioidosis										X	X	X	X				X			X											
MRSA	X	X				X	X			X			X	X	X																
Mycobacteriosis other than TB			X	X	X			X		X			X																		
TB	X	X								X			X			X														X	X

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Pasteurellosis	X	X																												
Plague	X	X					X	X													X	X								
Q Fever	X	X			X	X				X	X	X	X	X				X		X		X		X	X			X		X
Rat-bite fever	X	X	X					X										X			X	X	X							
Rocky Mountain spotted fever	X						X														X	X						X		
Salmonellosis	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X			X			X
Tularemia	X	X		X			X	X	X	X		X	X							X	X			X				X		X
Yersiniosis	X	X			X	X	X							X																
Fungal																														
Cryptococcosis																						X								
Dermatophytosis	X	X	X		X	X	X		X	X	X	X	X					X	X	X		X					X	X		X
Sporotrichosis	X	X							X	X	X		X			X	X					X			X					
Histoplasmosis																					X				X					
Parasitic																														
Baylisascariasis	X						X											X		X	X									
Chagas' disease (trypanosomiasis)	X	X																X	X	X				X		X	X			X
Cysticercosis (*Taenia* infection)							X							X						X					X	X				X
Cryptosporidiosis	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X		
Dipylidiasis	X	X																			X									
Dirofilariasis	X	X															X								X	X				
Echinococcosis	X						X		X	X	X	X	X			X		X			X						X		X	X
Giardiasis	X	X							X	X	X	X	X																X	
Hookworm infestation	X	X									X										X				X	X				
Leishmaniasis	X	X				X			X							X					X			X						
Toxocariasis	X	X									X		X	X	X		X				X				X	X				X
Toxoplasmosis	X	X			X	X			X			X	X	X				X	X		X	X						X		
Trichinellosis	X												X					X						X		X	X			
Prion																														
Transmissible spongiform encephalopathy	X								X			X			X														X	X
Viral																														
Hantavirus infection								X										X												
Herpes B																														

Table 9-3 ■ Chart of Species and Associated Pathogens—cont'd

Disease	Dogs	Cats	Ferret	Reptiles and amphibians	Caged birds	Rabbits	Pocket pets (rodents)	Fish	Horses	Cattle	Goats	Sheep	Swine	Poultry	Mink	Nonhuman primates	Camels, llamas, alpacas	Raccoons	Squirrels	Other wild rodents	Wild birds	Marine mammals	Wild cats	Foxes, coyotes, wild canids	Bats	Skunks	Opossums	Elephants	Beavers	Deer	Other wild herbivores
	Domestic																														
Influenza (human)			X										X																		
Influenza (avian)	X	X	X		X	X							X	X	X	X					X		X	X							
Lymphocytic choriomeningitis	X					X	X						X			X															
Monkeypox						X	X									X			X												
Orf											X	X																			X
Rabies	X	X	X			X			X	X	X	X	X		X	X		X	X				X	X	X	X				X	
Rift Valley fever	X	X								X	X	X					X	X	X	X											X
West Nile virus infection	X	X			X	X			X		X	X							X	X					X	X					

Adapted from Kahn CM, Line S (eds): *The Merck veterinary manual*, ed 9, Whitehouse Station, NJ, 2005, Merck; Dvorak GA, Rovid-Spickler A, Roth JA (eds): *Handbook for zoonotic diseases of companion animals*, The Center for Food Security & Public Health, Ames, IA, 2006, Iowa State University; Forrester DJ: *Parasites and diseases of wild mammals in Florida,* Gainesville, FL, 1992, University Press of Florida.
MRSA, Methicillin-resistant *Staphylococcus aureus; TB*, tuberculosis.

ANTHRAX

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Cutaneous anthrax (ICD-10 A22.0), Pulmonary anthrax (A22.1), Gastrointestinal anthrax (A22.2)

Other names in humans: wool sorter's disease, charbon, malignant carbuncle, Siberian ulcer

Other names in animals: splenic fever, Milzbrand

Anthrax is a fatal disease of herbivores. Most human cases result from direct contact with sick or dead animals or contaminated animal products. The causative agent, *Bacillus anthracis*, is a Centers for Disease Control and Prevention (CDC) Category A bioterrorism agent, and the anthrax-tainted letters mailed in the United States in 2001 were a reminder of its potential for deliberate release. In the United States, anthrax outbreaks in wildlife and livestock occur annually but human cases are rare.[1] Veterinary and human health care professionals need to recognize the clinical signs of disease and report suspected cases to public health authorities.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Characterize the risk in the community, including whether cases have been reported in livestock or wildlife and whether there is a possibility of environmental contamination.
- Work with veterinary authorities to control disease in animals.
- Conduct immediate investigation of human cases to determine whether they are related to zoonotic transmission or deliberate toxin release.
- Ensure that potentially exposed individuals receive postexposure prophylaxis (PEP).
- Counsel people who contact spores to wash hands with soap and water, followed by an organic iodine solution immersion. Clothing should be washed and boiled.
- Recommend that imported animal hides be disinfected before use. The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) regulates importation of all animal hides but does not mandate screening of imported hides for *B. anthracis*. In addition, some hides may be imported illegally.[2]
- Reduce environmental exposure risk through disinfection where possible.
- Provide guidance for environmental sampling and environmental cleanup.[3,4]

Human Health Clinicians

- Consider the diagnosis in all patients with livestock contact or travel to endemic countries.
- Report suspicion of disease immediately to public health authorities.

- Counsel travelers to endemic areas about risk reduction and monitoring for symptoms.
- If providing occupational health services to workers at risk, ensure that they are educated about symptoms of the disease, use adequate protective equipment, and that efforts are taken to reduce potential of infection (such as disinfection of animal hides with formalin).
- Consider vaccine for high-risk groups,[5] including laboratory workers and persons who handle potentially infected animals and animal products in high-incidence areas where safety standards are insufficient to prevent exposure to anthrax spores.[6] Military personnel[7] deployed to areas with high risk for biological warfare may require vaccination.

Veterinary Clinicians

- Do not perform a necropsy on suspected animal cases.
- Annually vaccinate cattle, sheep, horses, goats, and swine in endemic areas using the Sterne strain vaccine.[8] Treat infected and potentially infected animals. During quarantine these animals should not be used as food.
- Report suspected cases to agricultural health authorities who can quarantine premises to prevent spread of disease.
- Veterinarians who work with potentially infected animals in high-incidence areas should consider vaccination.
- Avoid contact with blood and bloody discharges. Keep flies and scavengers from carcasses. Infected carcasses should be burned (preferred) to destroy spores or buried in quick lime. To kill spores use 2% glutaraldehyde or 5% formalin for several hours. Heat sterilization at 121°C for 30 minutes can also be used.
- Notify health department immediately if cases are diagnosed in animals. Such cases could both pose a risk to humans and be a sentinel warning of deliberate release of toxin.

Agent

The bacterium *B. anthracis* is a spore-forming, nonmotile, gram-positive bacillus 3 to 5 microns long. When the vegetative form is exposed to air, it sporulates to form infectious spores. The spores may survive for decades in soil (Figure 9-3).

Geographical Occurrence

National disease control programs have reduced the global incidence of anthrax. It remains common in some Mediterranean countries, localized areas of Canada and the United States, parts of Central and South America, central Asia, parts of sub-Saharan Africa, and western China.[9] An epizootic among cattle in South Dakota in 2000 resulted in 157 cattle deaths and one human case of cutaneous anthrax.[10] Human anthrax resulting from exposure to infected livestock remains rare in the United States but occurs more commonly in less-developed countries. In many regions, the true incidence is not known because many cases in animals and humans probably go unreported.
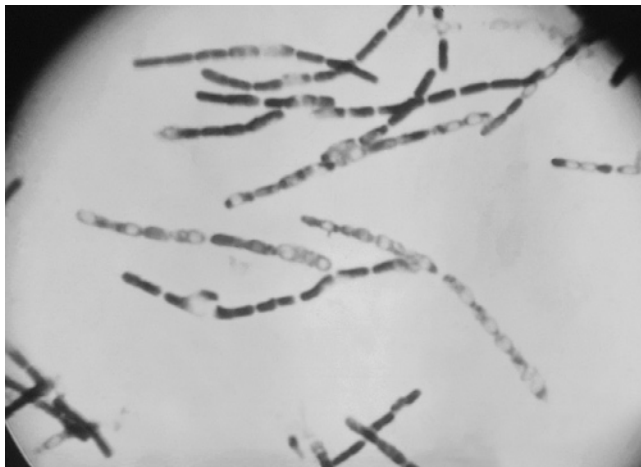
Figure 9-3 ■ Photomicrograph depicting a number of gram-positive, endospore-forming *Bacillus anthracis* bacteria.

Groups at Risk

Anthrax can be an occupational disease of workers who process carcasses and hides of infected animals, including farmers, abattoir workers, butchers, and workers in factories that process hides. Veterinarians who handle sick animals are also at risk, as are laboratory workers who routinely work with *B. anthracis*. Cases of both inhalation and cutaneous anthrax have developed in travelers and drum makers who have bought drums or hides originating from infected animals. In 2007, two cases of cutaneous anthrax in Connecticut were tied to importation of infected goat hides for drum-making (Figure 9-4).[2]

Figure 9-4 ■ *Bacillus anthracis*–contaminated drum head made from goat hide from Guinea; Connecticut, 2007. (From Centers for Disease Control and Prevention: Cutaneous anthrax associated with drum making using goat hides from West Africa—Connecticut, 2007, *MMWR Morbid Mortal Weekly Rep* 57(23):628, 2008.)

In the 2001 intentional use of anthrax in mail, postal workers were an occupational risk group. No animals were affected in these attacks.

Hosts, Reservoir Species, Vectors

The reservoir for anthrax is the environment, where the spores can survive for years in alkaline calcium-rich soil. Anthrax is principally a disease of livestock, including cattle, sheep, goats, and camels. Wild ruminants such as antelope and bison can also be infected and pose a risk to livestock.[11] However, all mammals are susceptible,[12] and horses, pigs, dogs, cats, and humans can be incidentally infected. Because of their higher body temperatures birds are normally resistant, but ostriches are susceptible. In some settings, biting flies may serve as vectors for anthrax transmission.[9]

In the 1979 accidental release of aerosolized anthrax in Sverdslovsk, Russia, cattle and sheep died as far as 50 km downwind from the release site, while human cases of inhalation anthrax occurred only up to 4 km downwind from the release.[13] The fact that animals became sickened over a wider geographical area than did humans may reflect their increased susceptibility and increased exposure risk, making animal cases sentinels for human risk.

Mode of Transmission and Life Cycle

Infected animals release vegetative bacteria into the environment. As the bacteria are exposed to air, they sporulate and the spores can survive for years. Ruminant animals grazing on areas contaminated by spores can ingest the spores and become infected. This can lead to further contamination of the environment and additional animal cases (Figure 9-5). Biting flies appear to play a role in large outbreaks by facilitating animal-animal transmission, sometimes over significant distances (5 to 15 km). Direct animal-animal transmission among herbivores is considered insignificant,[9] but if carnivores eat the flesh of infected animals, they can become infected.

Transmission from animal to human usually involves direct contact with spores because the vegetative form of the microbe is not as infectious. Spores may be present on an infected animal's hide, in meat that has been in contact with air and has developed spores, or as an aerosol from infected animal hide or tissues or from the environment.

Most human infection occurs through direct contact with animals or animal products. Such transmission is more likely when there are breaks in the skin and leads to the cutaneous form of the disease (Figure 9-6).

Airborne transmission from animals to humans can occur when spores are aerosolized during the processing or handling of contaminated animal hair, wool, hides, and bones. Improvements in working conditions have reduced this risk. Airborne transmission can also occur during the deliberate release of the agent.

Humans can also become infected through ingestion of tissue from an infected animal, leading to development of gastrointestinal or oropharyngeal anthrax. Human-to-human transmission is considered rare and has been reported only with cutaneous anthrax.
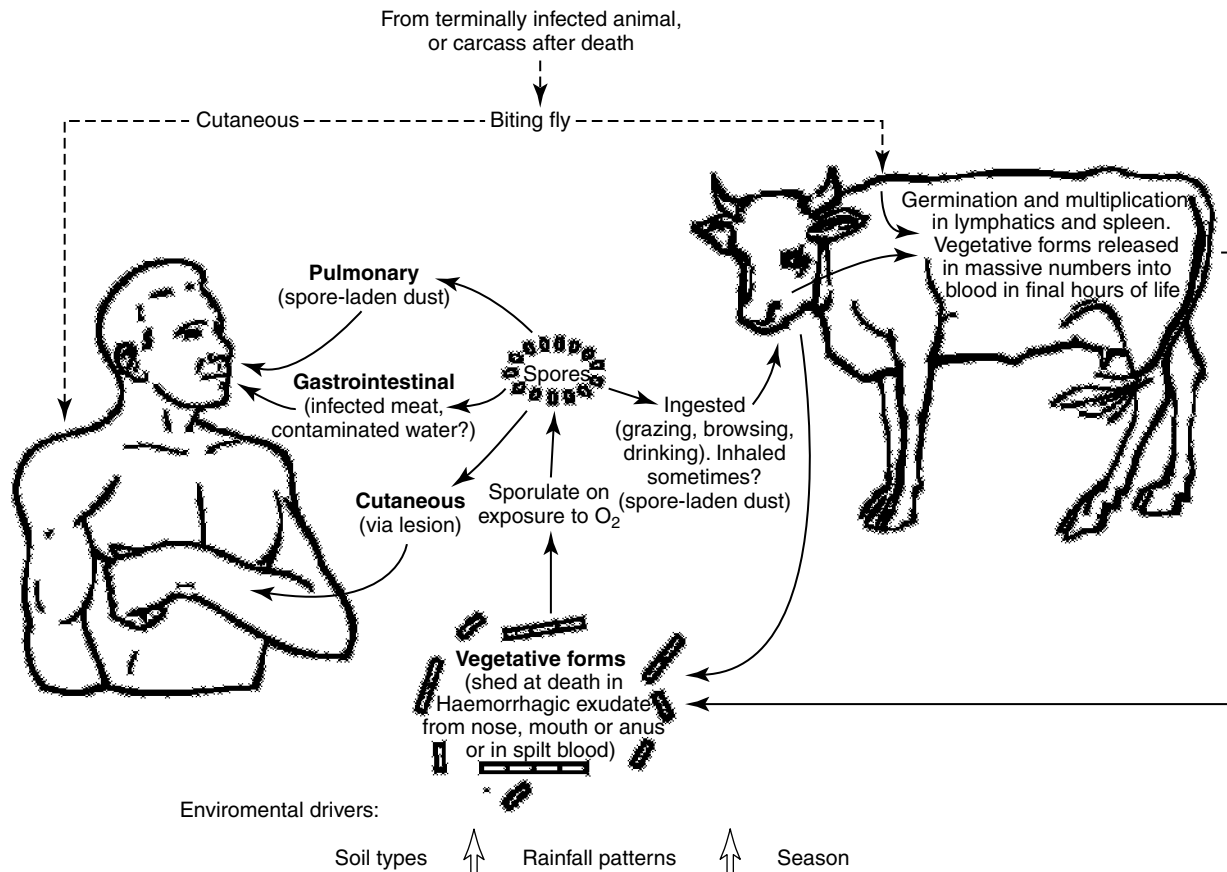
Figure 9-5 ■ Cycle of anthrax infection. (Modified from *Guidelines for the surveillance and control of anthrax in humans and animals*, ed 4, Geneva, 2008, World Health Organization. Available at http://www.who.int/csr/resources/publications/anthrax/whoemczdi986text.pdf.)
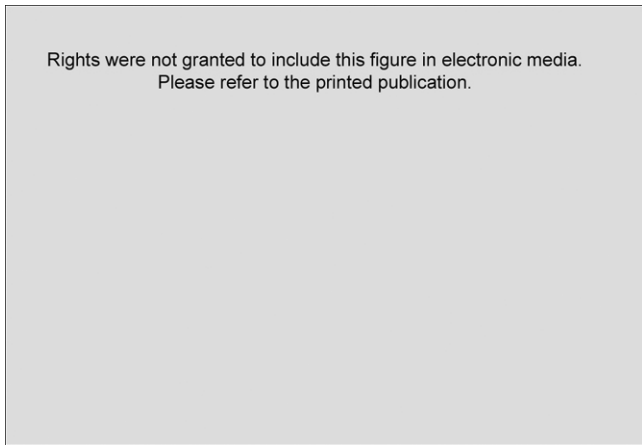

Figure 9-6 ■ Cutaneous anthrax in a child. (From Roche KJ, Chang MW, Lazarus H: Images in clinical medicine: cutaneous anthrax infection, *N Engl J Med* 345:1611, 2001.)

Environmental Risk Factors

The persistence of spores in the environment depends on a number of factors, including temperature, humidity, soil pH, calcium and other cations in soil, and the abundance of soil bacteria that could break down spores.[14] Outbreaks in wild-life species have been linked to climate factors such as hot, dry weather following spring flooding.[11] Heavy rainfall may increase the population of biting flies that can amplify animal outbreaks and may lead to spores being brought to the soil surface.[9,12]

Anthrax spores can contaminate indoor environments. One of the recent cases in Connecticut tied to imported drum hides was the child of the drum maker, who became infected through contamination of the household environment.[2]

Disease in Humans

There are three main forms of the disease: cutaneous, inhalational, and gastrointestinal. In naturally occurring human disease, more than 95% of cases are the cutaneous form. Inhalational anthrax is the next most common form. Gastrointestinal anthrax has never been reported in the United States. Table 9-4 shows the comparative clinical presentations of anthrax in humans and animals.

Cutaneous Anthrax

Cutaneous anthrax begins 1 to 7 days after inoculation with a small, painless, pruritic papule that is often asymptomatic and does not lead to an infected individual seeking medical

Table 9-4 ▪ Anthrax: Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Signs and Symptoms	Diagnostic Findings
Humans: *cutaneous* (95% of naturally occurring human cases)	Contact with infected animal or animal products	2-6 days	Painless, pruritic papule followed by vesicles, edema, ulcer, and eschar; bacteremia	Organisms seen on methylene blue stain, culture, or by PCR or ELISA
Inhalational	Aerosol from processing hides, wool, deliberate release	4-6 days	Malaise, fever, cough, followed by acute onset of respiratory distress	Chest radiograph may show widened mediastinum, pleural effusion
Gastrointestinal	Ingestion of infected meat	3-7 days[9]	Fever, abdominal pain, nausea, vomiting, bloody diarrhea, oropharyngeal swelling	Identification of bacteria in blood or other fluid samples
Cattle, sheep goats, other herbivores	Grazing on areas contaminated by spores, biting flies	1-20 days	Fever, depression, staggering, collapse, edema, abortion, sudden death	Demonstration of bacteria by culture, PCR, fluorescent antibody of blood or tissue
Pigs	Contact with contaminated soil	7-14 days	Often a milder form of disease with systemic symptoms and cervical lymphadenopathy Acute septicemia with oropharyngeal swelling and death may occur	Demonstration of bacteria by culture, PCR, fluorescent antibody of lymphoid or other tissue
Dogs, cats, wild carnivores	Ingestion of tissue from infected animal	1-14 days	Resembles disease in pigs	
Horses	Grazing on contaminated pasture	1-20 days	Fever, colic, diarrhea, swelling of neck, belly, genitalia	

ELISA, Enzyme-linked immunosorbent assay; *PCR*, polymerase chain reaction.

care. Over a period of days, vesicles develop with surrounding edema, which then rupture to form an ulcer covered by a black eschar. A significant degree of edema develops around the eschar and can be severe. Most cutaneous lesions are on the hands and arms. If the head and neck are involved, breathing may be compromised by the swelling. Bacteremia can develop, leading to systemic complications. Without antibiotic treatment the mortality rate is approximately 20%.[15] Figure 9-6 shows cutaneous anthrax in a child.

Inhalational Anthrax

Inhalational anthrax often begins with nonspecific malaise, mild fever, and nonproductive cough 1 to 6 days after exposure. After several days, a second phase of the disease begins abruptly with high fever, dyspnea, cyanosis, and stridor. A hemorrhagic lymphadenitis can develop with mediastinal widening (Figure 9-7). Without treatment, respiratory decompensation soon occurs. In up to half of cases, anthrax meningitis may also be present, with meningeal signs and altered consciousness.[15] Mortality rate is high even with antibiotic treatment.

Gastrointestinal Anthrax

Gastrointestinal anthrax is characterized by fever, abdominal pain, and bloody diarrhea that develop 2 to 5 days after ingestion of contaminated meat (to date, it has not been reported in the United States). Oropharyngeal involvement can produce swelling with respiratory compromise. The mortality rate can be 25% to 75%.[16]

Rights were not granted to include this figure in electronic media. Please refer to the printed publication.

Figure 9-7 ▪ Chest radiograph of a patient with inhalational anthrax in 2001. The *arrows* emphasize the widened mediastinum caused by the characteristic mediastinal adenopathy. (From Borio L, Frank D, Mani V et al: Death due to bioterrorism-related inhalational anthrax: report of 2 patients, *JAMA* 286:2554, 2001.)

Disease in Animals

Cattle and sheep develop an acute form of anthrax that is usually rapidly fatal. Clinical signs include fever, depression, staggering, difficulty breathing, and collapse. Subcutaneous edema may be present. Pregnant animals may abort before dying.

Infected horses can also develop acute disease with fever, colic, diarrhea, weakness, and swelling of the neck, sternum, belly, and genitalia. The disease is also rapidly fatal.

Pigs are considered to be more resistant to the disease compared with ruminants. Although pigs may develop an acute septicemia with sudden death and/or oropharyngitis with throat swelling and suffocation, a chronic form of disease is more common, with mild systemic signs and cervical lymphadenopathy.

Dogs, cats, nonhuman primates, and wild carnivores can develop disease resembling that in pigs (Figure 9-8).[15]

Diagnosis

Diagnosis in Humans

The differential diagnosis of cutaneous anthrax in humans includes boils, cellulitis, spider bite, rickettsial disease, ulceroglandular tularemia, rat-bite fever, leishmaniasis, and human orf. A history of exposure to livestock or livestock products, the presence of extensive edema, and the lack of pus and pain can provide clues to the diagnosis.

Inhalational anthrax can present with nonspecific symptoms and may be confused with other causes of pneumonitis, including community-acquired pneumonia and influenza. In the second, severe stage of illness, possible considerations include aortic dissection, pneumonic plague, and hantavirus pulmonary syndrome. A screening protocol for

Figure 9-8 ■ Gross pathologic posterior oblique view of inhalation anthrax in a chimpanzee's lungs. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy U.S. Army, Arthur E. Kay.)

inhalation anthrax has been proposed by a consensus report (Figure 9-9). This protocol is based on history of exposure and the presence of clinical signs.

Gastrointestinal anthrax, though rare, typically presents as a cluster of cases of acute abdominal pain and diarrhea following ingestion of food from a common source. It can
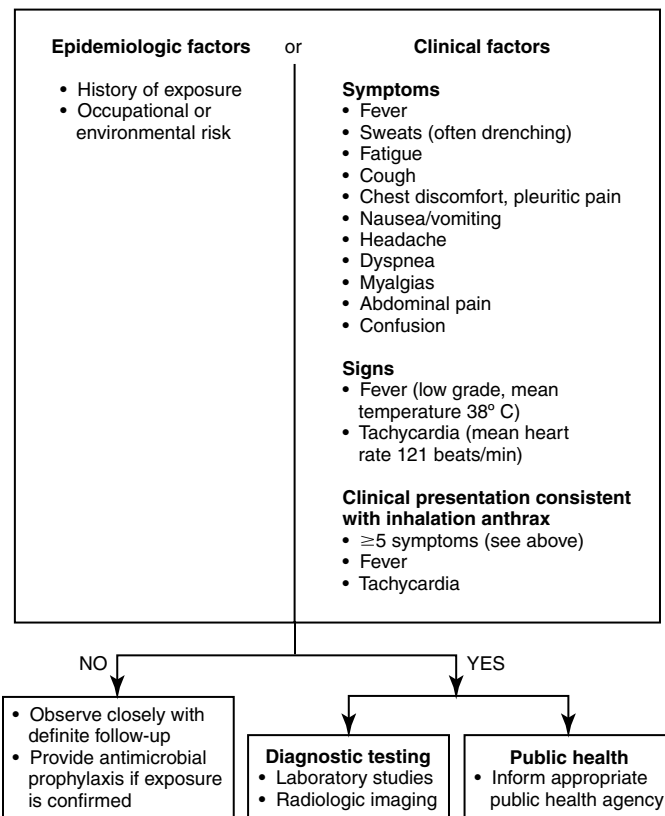
Figure 9-9 ■ Revisions to the Centers for Disease Control and Prevention (CDC) interim inhalation anthrax screening guidelines. (From Stern EJ, Uhde KB, Shadomy SV et al: Conference report on public health and clinical guidelines for anthrax, *Emerg Infect Dis* 14(4):pii: 07-0969, 2008.)

therefore be confused with other causes of food-borne illness.

The differential diagnosis of oropharyngeal anthrax includes streptococcal pharyngitis and Ludwig's angina.[9]

The laboratory diagnosis of anthrax involves identification of the capsulated organism in blood or tissues using methylene blue (M'Fadyean)-stained smears or through bacterial culture of blood or other specimens.[16] Rapid tests that are increasingly available include polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and immunohistochemical staining. Diagnostic testing for suspected inhalation anthrax in humans should include chest radiography and/or chest computed tomographic (CT) scanning to look for mediastinal widening.[1]

Diagnosis in Animals

In cattle, anthrax can be confused with other causes of sudden death, including lightning strikes, poisonings, leptospirosis, anaplasmosis, and clostridial infections. In pigs, other diagnoses to consider include classical or African swine fever and pharyngeal malignant edema. In dogs, other systemic infections or causes of pharyngeal edema should be considered.

Diagnostic testing can be performed on a swab of blood that is allowed to air-dry, resulting in sporulation of the bacteria and death of other bacteria and contaminants. In pigs, lymph tissue should be sent for studies. Bacterial culture, PCR, and fluorescent antibody stains can demonstrate the organism in blood and tissues.[17]

Treatment

Treatment in Humans

Treatment of anthrax in humans involves treatment with antibiotics as soon as the disease is suspected or as PEP.

Table 9-5 shows the recommended initial treatment regimens. Although quinolones or doxycycline are first-line agents, if the infecting strain is found to be susceptible to penicillin, penicillin can be substituted.

Treatment in Animals

Control of anthrax in animals may involve a combination of vaccination, quarantine, PEP of subclinically exposed animals, antibiotic treatment, or euthanization of sick animals and disposal of carcasses by burning. Cattle at risk should receive a full course of antibiotics, followed by vaccination 7 to 10 days later. Vaccination and antibiotics should not be given concurrently. Animals under treatment should be moved to a new pasture that is free from possible contamination.

Carcasses of animals that have died of anthrax should not be necropsied or otherwise opened to prevent sporulation of the bacteria and further cycles of infection.

ADDITIONAL RESOURCES

CDC Advisory Committee on Immunization Practices Recommendations for Use of Anthrax Vaccine

- *Use of Anthrax Vaccine in Response to Terrorism* (2002)
  http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5145a4.htm
- *Use of Anthrax Vaccine in the United States* (2000)
  http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4915a1.htm
- *MMWR Notice to Readers: Occupational Health Guidelines for Remediation Workers at* Bacillus anthracis–*contaminated Sites—United States,* 2001-2002 (*MMWR* 6;51(35), 786-789, 2002)

Table 9-5 ▪ Initial Treatment of Anthrax in Human Beings and Animals

Species	Primary Treatment	Alternative Treatment
Humans:		
Cutaneous	Ciprofloxacin 500 mg PO bid *or* levofloxacin 500 mg IV/PO bid × 60 days *Children <50 kg:* ciprofloxacin 20-30 mg/kg/day divided q12h PO (maximum 1 gm/day) × 60 days *or* levofloxacin 8 mg/kg PO q12h × 60 days	Doxycycline 100 mg PO bid × 60 days *Children >8 yr and >45 kg:* doxycycline 100 mg PO bid × 60 days *<8 yr:* doxycycline 2.2 mg/kg PO bid × 60 days[18]
Inhalational and gastrointestinal	*Adult:* Ciprofloxacin 400 mg IV q12h or levofloxacin 500 mg IV q24h *PLUS* clindamycin 900 mg IV q8h *and/or* rifampin 300 mg IV q12h; treatment duration 60 days; switch to PO when able	*Children:* ciprofloxacin 10 mg/kg IV q12h or 15 mg/kg PO q12h *or* doxycycline (>8 yr and >45 kg) 100 mg IV q12h, *PLUS* clindamycin 7.5 mg/kg IV q6h and/or rifampin 20 mg/kg (maximum 600 mg) IV q24h; treatment duration 60 days[19]
Postexposure prophylaxis	Ciprofloxacin 500 mg PO bid *or* levofloxacin 500 mg PO q24h × 60 days *Children:* ciprofloxacin 20-30 mg/kg/day divided q12h × 60 days	Doxycycline 100 mg PO bid × 60 days *Children >8 yr and >45 kg:* doxycycline 100 mg PO bid *<8 yr:* doxycycline 2.2 mg/kg PO bid × 60 days
Cow, sheep, goat, horse	Penicillin	Oxytetracycline
Dog[19]	Oxytetracycline 5 mg/kg IV q24h Potassium penicillin G at 20,000 U/kg IV q8h	Enrofloxacin 5 mg/kg q24h

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5135a3.htm
- Bacterial Agents: Anthrax. In *Biosafety in microbiology and biomedical laboratories*, ed 5, pp. 122-124, 2007) http://www.cdc.gov/OD/OHS/biosfty/bmbl5/BMBL_5th_Edition.pdf

Antimicrobial Prophylaxis

- Antimicrobial Prophylaxis to Prevent Anthrax Among Decontamination/Cleanup Workers Responding to an Intentional Distribution of *Bacillus anthracis* (2002): http://emergency.cdc.gov/agent/anthrax/exposure/cleanupprophylaxis.asp
- Responding to Detection of Aerosolized *Bacillus anthracis* by Autonomous Detection Systems in the Workplace (*MMWR* 2004/53(early release);1-11, April 30, 2004) http://www.cdc.gov/mmwr/preview/mmwrhtml/rr53e430-2a1.htm

Personal Protective Equipment

- Protecting Investigators Performing Environmental Sampling for *Bacillus anthracis:* Personal Protective Equipment (Nov. 6, 2001): http://emergency.cdc.gov/agent/anthrax/environment/investigatorppe.asp
- Interim Recommendations for the Selection and Use of Protective Clothing and Respirators Against Biological Agents (Oct. 25, 2001): http://www.bt.cdc.gov/documentsapp/Anthrax/Protective/10242001Protect.asp

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BARTONELLA INFECTIONS

Peter M. Rabinowitz and Lisa A. Conti

Bartonella infection *(ICD-10 A28.1)*

Other names in humans: cat-scratch fever, cat-scratch disease, benign lymphoreticulosis, Parinaud's oculoglandular syndrome, bacillary angiomatosis, bacillary parenchymatous peliosis (peliosis hepatis), recurrent rickettsemia

Other names in animals: bartonellosis

Bartonella henselae, the causative agent for cat-scratch disease (CSD), is usually associated with self-limited infection in humans and subclinical disease in cats, but it is capable of serious systemic infection in humans. Other *Bartonella* species may be emerging pathogens for humans and other animals.

Bartonella infection is an occupational risk for veterinary workers (including one reported case of *Bartonella clarridgeiae*) and one of the more common infections associated with cat ownership.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Educate community about avoiding cat scratches and bites (particularly kittens), thorough cleaning of wounds to reduce infection, discouraging cats from licking a person's skin or opens wounds, and flea and tick control.[1]

Human Health Clinicians

- Be alert to diagnosis in persons with unexplained lymphadenopathy or fever of unknown origin.
- Counsel immunocompromised patients to avoid cat scratches, thoroughly clean wounds after a scratch or bite, and to not allow cats to lick a person's skin or open wounds.
- Consider risk of infection in any patient bitten or scratched by a cat or with flea or tick bites.
- Counsel occupationally exposed workers (e.g., zookeepers) and persons owning cats to avoid and seek care for bites and scratches and to be alert to signs and symptoms of infection.
- Report cases to health department if required in state.
- No human vaccine is currently available.

Veterinary Clinicians

- Ensure flea control for cats.
- Counsel cat owners, especially immunocompromised patients, about avoiding cat scratches and bites, thorough cleaning of cat infected wounds, and not allowing cats to lick a person's skin or open wound. Although declawing has not been associated with preventing infection, some recommend trimming cats' nails routinely. Some suggest keeping cats indoors.
- A vaccine has been developed (though not currently marketed).

Agent

B. henselae is a gram-negative bacillus in the family Bartonellaceae. This family shares some features with rickettsial organisms but has been removed from the order Rickettsiales. The genus *Bartonella* includes at least 20 species, five of which (*B. henselae, B. quintana, B. bacilliformis, B. vinsonii* subspecies *arupensis,* and *B. elizabethae*) are recognized human pathogens (Table 9-6).[2] At present, no animal reservoirs of *B. quintana* or *B. bacilliformis* have been identified. *B. henselae, B. vinsonii,* and *B. elizabethae* are known to infect both human and animal hosts.[3]

Geographical Occurrence

B. henselae is found worldwide.

Groups at Risk

CSD can be an occupational disease of veterinarians and others providing care to cats. Studies of zookeepers have revealed seroprevalence rates for past *Bartonella* infection as high as 65%,[4] while a convenience survey of veterinarians and veterinary workers found *Bartonella* species seroprevalence of only 7%.

Hosts, Reservoir Species, Vectors

Bartonella species have been found in a wide range of subclinically infected mammals, including rodents, rabbits, deer, elk, bighorn sheep, cattle, foxes, dogs, and coyotes.[5] Domestic cats are considered the principal reservoir for *B. henselae*.[6] Seroprevalence studies have shown rates of antibody positivity in cats in the range of 40%.[7] However, infection in cats is considered either subclinical or subtle, even in the setting of chronic bacteremia. *B. henselae* has also been isolated from cat fleas, dog fleas, and a number of other vectors.[8] Dogs may also be infected with *B. henselae*. Recent data show that ticks may play a role in transmission to humans.[9]

B. quintana at present is known to have only a human reservoir and is spread by the human body louse. *B. vinsonii* and *B. elizabethae* have been found in asymptomatic rodent reservoirs, including rural mice (*B. vinsonii*)[10] and urban rats (*B. elizabethae*).[11] Infection to humans may occur through vectors or direct contact.

Mode of Transmission and Life Cycle

Despite the fact that *B. henselae* can occur in vectors, transmission to humans is thought to be mainly mechanical

Table 9-6 ▪ Pathogenic *Bartonella* Species

Bartonella Species	Disease(s)	Reservoir(s)	Arthropod Vector(s)
B. bacilliformis	Oroya fever and verruga peruana	Humans	Sandflies
B. clarridgeiae	Cat-scratch disease; canine valvular endocarditis	Domestic cats	?
B. elizabethae	Human endocarditis	Norway rat	?
B. grahamii	Human neuroretinitis	Rodents	Fleas
B. henselae	Human, canine cat-scratch fever, endocarditis, peliosis hepatitis	Domestic cats; dogs (?)	Cat flea
B. quintana	Human trench fever	Humans	Body lice
B. vinsonii subsp. *arupensis*	Human endocarditis	Mice, voles	?
B. vinsonii subsp. *berkhoffii*	Human, canine endocarditis; canine granulomatis lymphadenitis, rhinitis, peliosis hepatitis	Rodents, dogs	Ticks
B. washoensis	Human myocarditis	Ground squirrels	?

From Songer JG, Post KW: *Veterinary microbiology: bacterial and fungal agents of animal disease*, St Louis, 2005, Saunders Elsevier.

through a scratch or bite or licking of an open wound or rubbing the eyes with contaminated hands (Figure 9-10). The role of fleas in transmission is not well understood.

Environmental Risk Factors

Flea infestation is a definite risk factor for both feline and zoonotic infection because cats infested with fleas have higher seroprevalence of *Bartonella* infection.

Disease in Humans

Cat scratch infection produces an inoculation at the point of injury, with inflammation of nearby lymph nodes several weeks later (Color Plate 9-2). The lymph swelling often is self-limited over a period of months in immunocompetent hosts (Figure 9-11). In up to one sixth of cases the lymph nodes suppurate. Other symptoms can include malaise, fatigue, fever, and rash.[3]

Atypical presentations of *B. henselae* infection include Parinaud's oculoglandular syndrome (granulomatous conjunctivitis accompanied by pretragal lymphadenopathy).[3] Even in immunocompetent patients, serious complications of *B. henselae* infection can occur, such as central nervous system (CNS) involvement (including encephalopathy and myelitis)[12]
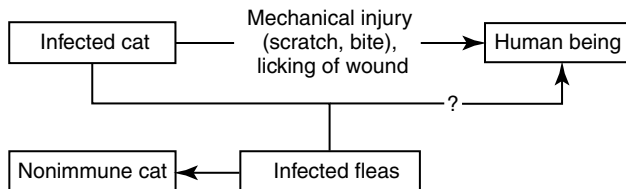
Figure 9-10 ▪ Life cycle of *Bartonella henselae* infection.

Figure 9-11 ▪ Papular lesion and enlarged lymph nodes in a person with cat scratch disease. (From Long SS, Pickering LK, Prober CG (eds): *Principles and practice of pediatric infectious diseases,* ed 3, Philadelphia, 2008, Saunders Elsevier.)

and hepatic abscesses. In many but not all cases, CSD precedes the development of more serious complications. In the elderly, *B. henselae* endocarditis may be found more frequently (a common cause of culture-negative endocarditis), whereas CSD is less frequent than in younger individuals.[12]

In immunocompromised individuals, complications of infection can include bacillary angiomatosis (Color Plate 9-3). Peliosis hepatis, a condition characterized by fever, chills, hepatosplenomegaly, and gastrointestinal symptoms, can develop in immunocompromised patients. Like *B. henselae*, *B. quintana* causes a number of conditions, including trench fever, endocarditis, bacillary angiomatosis, and peliosis hepatitis.[11]

At present, case reports of bacteremia and endocarditis in humans resulting from infection with *B. vinsonii*[10] and *B. elizabethae* are limited.[13] Antibodies to *B. elizabethae* have been found in urban homeless and drug users,[14] but the clinical significance remains poorly understood.

Disease in Animals

B. henselae causes subclinical infection in cats, including chronic bacteremia. Between 5% and 60% of cats may be seropositive depending on the geographical area. There is a case report of *B. henselae* infection in a Golden Retriever causing pelosis hepatitis (Figure 9-12 and Color Plate 9-4).[15] Table 9-7 provides comparative clinical manifestations in humans and other animals.

Diagnosis

Diagnosis in humans is based on the clinical picture of local lymphadenopathy, especially in the setting of a history of cat contact. *Bartonella* species are difficult to grow in culture; therefore other diagnostic techniques such as PCR and serology are often required (e.g., immunofluorescent antibody [IFA] titer ≥1:64 to *B. henselae*).[19] Cross-reactions can occur among *Bartonella* species and *Chlamydia* and
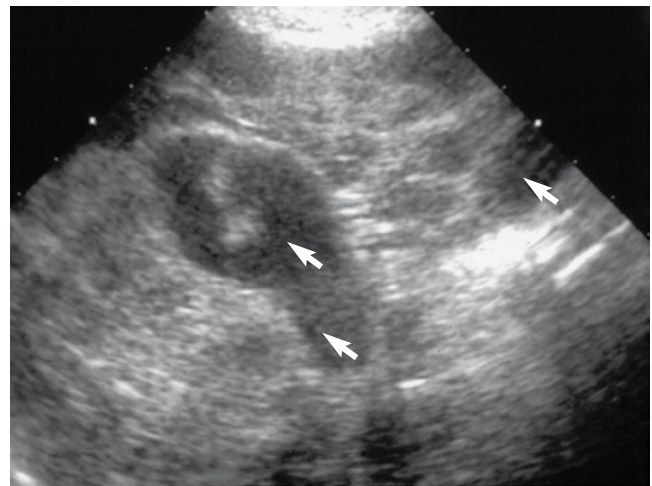

Figure 9-12 ▪ Ultrasonographic appearance of the liver of a dog with peliosis hepatis associated with *B. henselae* infection showing hypoechoic areas *(arrows)* representing vascular peliosis. (From Greene CE: *Infectious diseases of the dog and cat,* ed 3, St Louis, 2006, Saunders Elsevier. Courtesy Barbara Kitchell, University of Illinois, Urbana, Ill.)

Table 9-7 ▪ *Bartonella* Infections: Comparative Clinical Presentations in Humans and Other Animals[16]

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
B. Henselae				
Humans	Cat scratch or bite, immunocompromised individuals at increased risk	3-10 days	Lymphadenopathy, fever, culture-negative endocarditis; rare complications including bacillary angiomatosis, neurological involvement, endocarditis, Parinaud's oculoglandular syndrome	Leukocytosis, elevated sedimentation rate, serology (IFA or ELISA), PCR
Cats		2-16 days (experimental infection)	Subclinical or mild symptoms, uveitis (?)	Blood culture, serology (IFA)
B. Vinsonii Subsp. Berkhoffii				
Humans			Bacteremia and endocarditis reported[17]	
			Isolated in healthy animals	
Dogs and coyotes			Canine granulomatous rhinitis (?), liver disease, endocarditis, fever, death	
B. Vinsonii Subsp. Arupensis				
Humans	Rodent exposure (?)		Bacteremia, endocarditis reported[18]	
Rodents			Subclinical	
B. Elizabethae				
Humans	Rodent exposure[14]		Endocarditis reported[13]	
Rodents			Subclinical	

ELISA, Enzyme-linked immunosorbent assay; *IFA*, immunofluorescent antibody; *PCR*, polymerase chain reaction.

Coxiella. PCR of tissue and fluid obtained from lymph node biopsy can often identify the organism. Disease in animals can be diagnosed by blood culture or serology (IFA or ELISA) and PCR.

Treatment

In humans, some cases of CSD in an immunocompetent host may not require antibiotic treatment.[12] However, any immunocompromised patient, as well as any patient with extralymphatic involvement, should be treated with antibiotics.[20] Table 9-8 outlines treatment guidelines for symptomatic disease in humans. There are no treatment protocols for animals.

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Table 9-8 ▪ *B. Henselae* Treatment in Humans and Other Animals[21]

Species	Primary Treatment	Alternative
Humans		
Cat-scratch disease (immunocompetent)	*Adults:* azithromycin 500 mg × 1, then 250 qd × 4 days *Children* (≤45.5 kg): liquid azithromycin 10 mg/kg ×1, then 5 mg/kg/day × 4 days[12]	Consider no treatment since often self-limited
Bacillary angiomatosis, peliosis hepatitis, immunocompromised patients	Clarithromycin 500 mg bid or clarithromycin ER 1 gm PO q24h *or* azithromycin 250 mg q24h *or* ciprofloxacin 500-750 mg PO bid × 8 wk[12]	Erythromycin 500 mg PO qid *or* doxycycline 100 mg PO bid × 8 weeks, or if severe, combination of doxycycline 100 mg PO/IV bid and rifampin 300 mg PO bid
Cats, Dogs (With Clinical Signs)	Azithromycin 5-10 mg/kg once a day × 7 days and every other day × additional 5 weeks[22]	

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BRUCELLOSIS

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Brucellosis due to Brucella melitensis (ICD-10 A23), Brucellosis due to Brucella abortus (A23.1), Brucellosis due to Brucella suis (A23.2), Brucellosis due to Brucella canis (A23.3)

Other names in humans: undulant fever, Mediterranean fever, Malta fever

Other names in animals: Bang's disease (cattle), epizootic abortion, contagious abortion

Brucellosis is an important bacterial disease of ruminants worldwide and an occupational disease for humans working closely with infected animals. Many human cases are related to foodborne exposures to unpasteurized dairy products. Brucellosis prevention demands a "One Health" approach between animal and human health disciplines because the human health risk can be reduced only by controlling the disease in animals.[1] Brucellosis can be passed between domestic cattle and wildlife such as bison, where it can be difficult to control.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Describe the local incidence and prevalence in human, domestic animal, and wildlife populations using cooperative veterinary/human disease surveillance systems.[2]
- In endemic areas, coordinate with local agricultural and wildlife agencies regarding vaccination, testing, and control in domestic livestock and wildlife.

- Educate the public (especially travelers to endemic countries) on risk of infection from unpasteurized dairy products.
- Encourage public health measures to avoid consumption of unpasteurized dairy products.
- Educate hunters of feral swine and other potentially infected wildlife (e.g., elk, bison) about infection control precautions, including gloves and protective clothing while preparing carcasses and burying of all remains to avoid scavenging.
- If disease is present in livestock population, educate farmers and livestock workers regarding personal protection when handling strain 19 vaccine, potentially infected tissue, and adequate ventilation in abattoir environments.
- Sentinel human cases may indicate problems with food safety, infection in local livestock, or inadequate safety controls for workers and require public health follow-up.
- Educate local veterinary and human health clinicians about groups at risk, signs of disease, and to consider the possibility of intentional exposure activity.

Human Health Clinicians

- Screen for exposure risk factors: ingestion of unpasteurized dairy products, contact with potentially infected animals, recent travel to endemic areas, and animal contact during travel.
- Human cases should immediately be reported to local health officials.
- When treating human cases, while rarely transmitted person to person, counsel about safe sex precautions to prevent secondary transmission.
- Ensure that workers in high-risk occupations (including veterinarians and laboratory workers) are using appropriate biosafety procedures.

- Consider brucellosis in workup of fever of unknown origin.
- Offer PEP and management to exposed laboratory workers and veterinary workers with vaccine exposure.
- Counsel patients to avoid consuming unpasteurized dairy products and to use protective clothing (rubber boots, gloves, goggles) if they must come in contact with infected livestock, wild ruminants, or wild dogs.
- Consider a 3- to 6-week prophylactic antibiotic course for a needlestick injury with a veterinary vaccine, laboratory, or bioterrorism exposure.[3]
- No human vaccine is available.

Veterinary Clinicians

- Isolate and screen herd replacements.
- Quarantine infected herds, test and slaughter to eradicate infection, and disinfect facility where infected animals have been housed.
- Report animals with positive screenings to agriculture officials.
- Vaccinate cattle, sheep, and goats against Brucella.*
- Ensure proper biosafety procedures are followed in veterinary facility and that staff are aware of symptoms of infection.
- If diagnosing animal case, discuss zoonotic risk with owner; offer direct communication with human health clinician caring for family.
- Disinfect with 1% sodium hypochlorite, 70% ethanol, or iodine solutions. Brucella can also be inactivated by several hours of direct sunlight.[3] Replacement swine herds can be placed on ground that has been free of pigs for a minimum of 30 days.

Agent

Brucellosis is caused by Brucella species, which are gram-negative coccobacilli. A number of species in the genus have affinities for particular animal hosts. These species have been further subdivided into biologically distinct strains (biovars).[6] At least four species of Brucella are found in animals and man; these include Brucella abortus (cattle), B. melitensis (goats), B. suis (swine),* and B. canis (dogs). There have been several reported isolations of bacteria from marine mammals, including seals, whales, and dolphins that are currently classified in the genus Brucella. However, the human zoonotic potential of these new agents remains to be established.[7]

Geographical Occurrence

Brucellosis is found worldwide, but its prevalence depends largely on the state of control in domestic animals. In the United States, bovine brucellosis control programs have reduced the frequency of infection in both cattle and humans.

Between 1986 and 2007, fewer than 150 human cases were reported annually in the United States.[8,9] As a result, many human health clinicians in the United States have never seen a case. In the United States, the highest incidence rates are in states bordering Mexico, including California and Texas. The most common Brucella species for human infections in the United States are B. abortus and B. melitensis.[10] The occurrence of human brucellosis is higher in other countries where livestock infection is not as well controlled, including Mexico, other Latin American countries, the Mediterranean basin, Eastern Europe, Asia, Africa, and the Middle East. The United Nations' Food and Agriculture Organization has set a goal for worldwide eradication of brucellosis.

Groups at Risk

Worldwide, brucellosis is considered largely an occupational disease of workers exposed to cattle and other large animals through animal husbandry, dairy, and slaughter operations. Such workers include herdsmen, slaughterhouse workers, and veterinarians. Handling of infected aborted fetuses and newborn animals is considered a particularly high-risk activity. Another risk is sharing living spaces with potentially infected animals; high rates of brucellosis infection have been reported among goat-herding families that bring goats into family bedrooms during the winter.[11]

A rare occurrence among veterinarians is the self-inoculation (needlestick, splash or spray to mucous membranes, or broken skin) of vaccine strains of Brucella (RB51 or B. abortus strain 19, or B. melitensis Rev-1) during animal vaccination; this represents one of the rare reported occupational risks of animal vaccination.[12] Outbreaks have occurred in laboratory workers who handled Brucella cultures outside biological safety cabinets,[9] and dog handlers are considered to be at risk from B. canis. However, analysis of recent cases in the United States indicates that brucellosis is increasingly a foodborne disease associated with ingestion of unpasteurized dairy products from infected animals.[10]

Hosts, Reservoir Species, Vectors

The species and biovars of Brucella are adapted to particular animals that serve as definitive hosts. However, as shown in Tables 9-9 and 9-10, cross-species infections can occur, with humans and dogs particularly susceptible to infection by a number of different Brucella species.

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*A number of vaccines are available for different animal species. In cattle, vaccination with B. abortus strain 19 or RB51 increases resistance to infection.[4] The same vaccines have been used to attempt to control outbreaks in wildlife species, including coyotes, elk, and bison.[5] Goats can be vaccinated with the Rev1 strain of B. melitensis. There is no vaccine for Brucellosis in swine. In dogs, brucellosis vaccine has not been found to be effective.[4]

Table 9-9 ■ Hosts for *Brucella* Species	
Species	**Animal Hosts**
Brucella abortus	Cattle, elk,[13] bison, water buffalo,[14] goats,[4] horses,[15] dogs,[4] coyotes[16]
Brucella melitensis	Goats, sheep, cows, dogs[4]
Brucella suis	Pigs, feral swine and wild boar, horses, cattle,[4] dogs[4]
Brucella ovis	Sheep
Brucella canis	Dogs

Table 9-10 ■ Brucellosis: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans (*B. abortus, B. melitensis, B. suis, B. canis*)	Ingestion of unpasteurized dairy products, occupational exposure to animal tissue, fluids, aerosol	Variable, usually 5-60 days[20]	Fever, joint pain, abdominal pain, weight loss, fatigue, arthritis, endocarditis, epididymitis/orchitis	Elevated IgG; other laboratory values may be normal or leukopenia, thrombocytopenia, abnormal liver function may occur; positive blood culture
Dogs (*B. canis, B. abortus, B. melitensis, B. suis*)	Ingestion of infected tissue Sexual contact Transplacental	Variable, related to stage of gestation, often months	Usually asymptomatic or vague signs, but lethargy, lymphadenopathy, back pain, weakness, glomerulonephritis, discospondylitis may occur[21] *Females:* abortion, infertility *Males:* Epididymitis, testicular atrophy	CBC usually normal, positive serology, positive blood or tissue culture
Sheep, goats (*B. melitensis, B. abortus*) Sheep (*B. ovis*)	Direct contact, sexual transmission	Variable, related to stage of gestation, often months	Abortion Epididymitis	Positive serology
Cattle (*B. abortus*)	Ingestion of contaminated tissue, feed, water	Variable, related to stage of gestation, often months	Abortion, epididymitis, arthritis	Positive serology, *Brucella* ring test
Swine (*B. suis*)	Ingestion of infected tissue, sexual contact	Variable, related to stage of gestation, often months	Abortion, orchitis, spondylitis, sterility[4]	Brucellosis card test

CBC, Complete blood cell count.

Mode of Transmission and Life Cycle

Brucellosis is transmitted by direct contact with infected tissues or secretions and enters the body by breaks in the skin or contact with mucous membranes (Figure 9-13). It can also be acquired by ingestion of contaminated foods. Aerosol transmission can easily occur. It is thought that a small number of inhaled organisms can lead to human infection, as seen in outbreaks
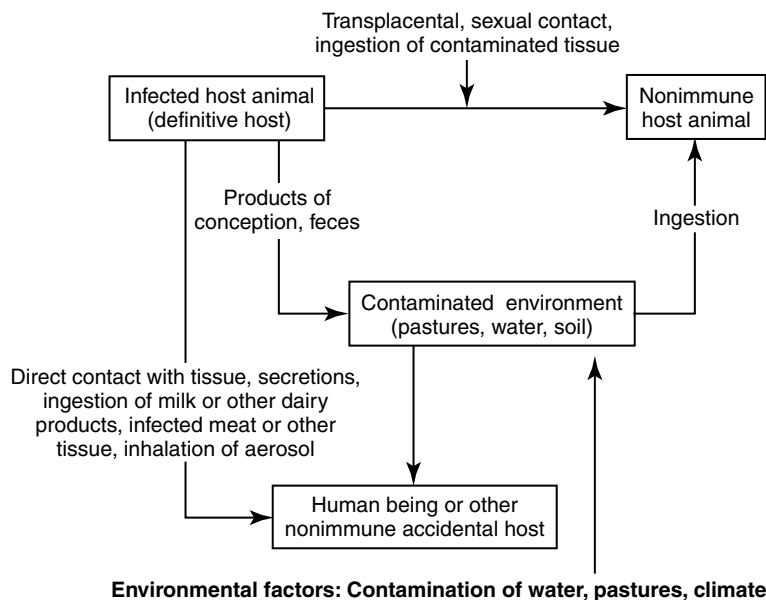
Figure 9-13 ■ Transmission and life cycle of *Brucellosis*.

of infection among laboratory workers. *Brucella* consequently requires biosafety level 3 containment in laboratories.

Transmission in cattle occurs through ingestion of contaminated pasture forage or water, as well as through licking and other direct contact of infected calves, fetuses, and afterbirths. Transmission in dogs is due to ingestion of or other contact with contaminated tissue, including sexual contact. The risk of transmission of brucellosis from dogs to humans is considered low and related to frequent close contact with blood, birth tissues, or other infected secretions.[17] In humans, person-to-person infection has been reported through breastfeeding, childbirth, bone marrow transplants, sexual contact, and transfusions, but these modes of transmission are considered exceptional.[6]

Environmental Risk Factors

Brucella may survive for months in the environment in water and other media that are not exposed to direct sunlight or heat. Pastures can become contaminated by feces, products of conception, and vaginal discharges of infected animals, leading to spread of infection in herds of grazing animals. *Brucella* organisms have been recovered from cow manure that has remained in a cool environment for longer than 2 months.[4]

Disease in Humans

Five to 60 days after infection, *Brucella* can cause a febrile illness that may be abrupt or gradual. Symptoms are often nonspecific and include fever, headache, night sweats, fatigue, arthralgia, myalgia, joint pain, anorexia, abdominal pain, diarrhea, vomiting, and weight loss. Depression may be a prominent feature. The fever may be "undulant" in patients who remain untreated. Clinical findings may be unremarkable, but in 20% to 30% of patients hepatosplenomegaly and/or lymphadenopathy may develop. Osteoarticular involvement of the spine and large weightbearing joints (Figure 9-14) is common.[18] Rarely, more severe infection can lead to epididymitis, orchitis, uveitis, endocarditis, and meningitis. A review of human cases found *B. melitensis* was more likely than *B. abortus* to cause abdominal pain and tenderness, hepatomegaly, splenomegaly, thrombocytopenia, pancytopenia, and hepatic dysfunction.[10] Laboratory findings are usually mild or absent but may include elevation of liver function test results, thrombocytopenia, and other hematologic abnormalities.

Disease in Animals

In most animals, spontaneous abortion is the most common manifestation of *Brucella* infection. Infection may be chronic and poorly responsive to treatment.

In pregnant cows, *B. abortus* causes placental infection leading to abortion in the second half of gestation. It also causes reduced milk yield, testicular abscesses and epididymitis in bulls, and (rarely) joint involvement with long-standing infection.[4] Infection in goats, sheep, and pigs is similar to that in cattle.

In sheep, *B. ovis* causes epididymitis in rams but abortions and stillbirths in ewes (Color Plate 9-5).[4]

Figure 9-14 ■ Radiograph of lumbar spine showing discitis and spondylitis due to brucellosis. Note reduced disk space and the destruction of articular margins at L3-L4 *(arrows)*. (From Cohen J, Powderly WG: *Infectious diseases*, ed 2, St Louis, 2004, Mosby Elsevier.)

Figure 9-15 ■ Fistulous withers in a horse. (From Auer JA: *Equine surgery*, ed 3, Philadelphia, 2006, Saunders Elsevier.)

Horses develop a rare bursitis condition known as *poll evil* or *fistulous withers* that may be caused by *B. abortus* or occasionally *B. suis* (Figure 9-15).[4]

In dogs, the most common recognized sign and symptom are abortion and infertility. Females may have a prolonged vaginal discharge following abortion. Lymphadenitis may

be seen. In males, orchitis, epididymitis, and prostatitis may occur. Spondylitis resulting in back pain and weakness, and uveitis are reported complications (Color Plate 9-6).[4]

Cats are apparently resistant to *Brucella* infection.[19]

Diagnosis

The differential diagnosis of brucellosis in humans is extensive and includes other causes of fever, including influenza, mononucleosis, human immunodeficiency virus (HIV), and malaria. A history of contact with animals, laboratory exposure, or consumption of unpasteurized dairy products should make clinicians suspect brucellosis. Diagnosis in humans is based on culturing the organism from blood, bone marrow, or other tissue, and/or serology. Cultures may be slow to grow and require caution in handling. Elevated immunoglobulin G (IgG) antibodies titers by ELISA or other tests including serum agglutination (SAT) are often key to the diagnosis, as active infection titers often exceed 1:160. Infection with *B. canis* may produce antibodies that do not react with standard *Brucella* test antigens; therefore specific *B. canis* serology must be requested if this infection is suspected. PCR techniques have shown promising results but are still in development.[21]

In dogs, cultures of blood and tissue are also used. There are several serological tests. The RSAT test has a high sensitivity but low specificity. The mercaptoethanol test also has low specificity; positive results must be confirmed by other tests such as the agar-gel immunodiffusion (AGID) test.[4]

Possible herd infection in cattle is diagnosed using the *Brucella* milk ring test, which is sensitive but not specific (Color Plate 9-7).[4] Blood samples are collected from slaughtered animals. Further tests are used to confirm positive results.

Postexposure Prophylaxis

Following laboratory or vaccine exposure to *Brucella* species, 100 mg of doxycycline twice daily and rifampin 600 mg/day should be taken for 21 days. Trimethoprin sulfamethoxazole is an alternative for those with a contraindication to doxycycline. Doxycycline alone should be given if the exposure was to *Brucella abortus* strain RB51, which is resistant to rifampin.[9] Baseline serum drawn for *Brucella* serology with repeat serology at 2, 4, 6, and 24 weeks can be used to monitor for evidence of infection. Such monitoring is not recommended for exposures to vaccine RB51, which does not elicit an antibody response on available assays. Exposed pregnant women should consult their obstetric care provider regarding PEP. Exposed persons should be monitored on a regular basis for the development of fever and other clinical signs of infection.[9]

Treatment

Antibiotic therapy for brucellosis infection in humans and other animals is outlined in Table 9-11 below. In humans, relapse and prolonged convalescence may occur after antibiotic treatment. Patients with focal complications including spinal or neurological involvement may require a more prolonged course of treatment.

Table 9-11 ▪ Brucellosis Treatment in Humans and Other Animals

Species	Primary Treatment	Alternative
Humans (adult or child >8 yr[23])	Doxycycline 100 mg bid × 6 wk *PLUS* gentamicin × 7 days *or* doxycycline 100 mg PO bid × 6 wk *PLUS* streptomycin 1 gm IM q24h × 2-3 wk	Doxycycline 100 mg PO bid *PLUS* rifampin 600-900 mg PO q24h × 6 wk *or* trimethoprim-sulfamethoxazole 1 DS tab (160 mg TMP) PO qid × 6 wk *PLUS* gentamicin × 2 wk
Humans (child <8 yr)	Trimethoprim-sulfamethoxazole 5 mg/kg PO q12h × 6 wk *PLUS* gentamicin 2 mg/kg IV/IM q8h × 2 wk[23]	
Postexposure prophylaxis	Doxycycline 100 mg PO bid *PLUS* rifampin 600 mg PO qd × 3 wk (doxycycline alone if exposed to strain *B. abortus* RB51)[9]	Trimethoprim-sulfamethoxazole (160 mg/800 mg) × 3 wk
Dogs	Doxycycline 12-15 mg/kg PO q12h × 4 wk *PLUS* gentamicin 5 mg/kg SC q24h at 0 and 1 wk[21]	

In animals, treatment can be unsuccessful even after prolonged administration of antibiotics. Therefore euthanasia and culling are often used as a means of brucellosis control. Animals may still be infectious to other animals (and humans) despite treatment, and this should be considered before attempting treatment of a pet dog. Neutering of infected dogs is sometimes performed to achieve infection control.

In cattle, antibiotic treatment is considered practical.[4]

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CAMPYLOBACTERIOSIS

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Campylobacter *enteritis (ICD-10 A 04.5)*

Other names in humans: Campylobacter *enteritis, vibriosis*

Other names in animals: bovine genital campylobacteriosis, vibriosis, epizootic infertility, epizootic ovine abortion

Campylobacter species (*C. jejuni* and *C. coli*) are now considered the leading cause of bacterial enteritis in humans (*Campylobacter* enteritis).[1] They are also found in a large number of animal species. Collaborative research between human health and veterinary researchers led to the relatively recent discovery of *Campylobacter* species as significant human pathogens. Improving diagnostic methods continue to shed light on the prevalence and clinical importance of *Campylobacter* species, including the high zoonotic potential of these agents.

Campylobacter fetus is associated with less common, but severe, infections in immunocompromised persons. Cattle, sheep, and goats are generally infected by contact with reproductive discharges and feces. *C. fetus* also is a sexually transmitted disease among cattle. Traditional culture methods for other *Campylobacter* may not detect *C. fetus*; therefore its true clinical importance remains poorly understood and probably underestimated.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Educate public (especially travelers to endemic countries) on the risk of infection from untreated drinking water, unpasteurized dairy products, and uncooked poultry, including handwashing and food preparation precautions.
- Educate food handlers to avoid cross-contamination of foods—use separate cutting boards.
- Pursue public health measures to control local consumption of unpasteurized dairy products.
- Prevent infected health care workers from providing direct patient care.
- Educate local human health and veterinary clinicians and public about risk of infection in puppies and kittens. Stress the need for handwashing and other hygiene after contact with pets and poultry. Prevent children from handling sick animals.
- Work with agricultural agencies and local farms to reduce incidence of *Campylobacter* in poultry at all phases of rearing and production.
- Educate local veterinary and human health clinicians about groups at risk and symptoms of disease and importance of handwashing for people with diarrhea.
- Coordinate with agriculture officials and veterinarians to receive information about outbreaks of *C. fetus* in local livestock herds so that agricultural workers can be educated about disease and need for biosafety on farms.

Human Health Clinicians

- Report cases to health department if required in state.
- Interview infected individuals about exposure risk factors, such as recent travel to developing country; ingestion of unpasteurized dairy products or undercooked meat; and contact with poultry or poultry products, dogs and cats (especially kittens and puppies), or other potentially infected animals. Notify public health authorities of ongoing risk to other humans.
- Counsel immunocompromised patients to avoid contact with puppies, kittens, dogs, and cats with diarrhea; poultry; unpasteurized dairy products; or undercooked meat.
- When treating an infected human, ensure enteric infection control precautions are used. Exclude the

symptomatic individual from food handling or care of sick individuals or contact with immunocompromised individuals. Stress proper hand hygiene.

• Ensure that workers in high-risk occupations (including poultry workers and veterinarians) use appropriate biosafety procedures, including handwashing.

• A candidate vaccine has been developed by the Navy Medical Research Institute.[2]

Veterinary Clinicians

• If treating an infected animal, counsel owner regarding zoonotic risk and need for adequate handwashing and disposal of feces. Offer direct communication with human health clinician caring for family.

• Discourage feeding raw diets to pets or allowing pets to hunt.

• Exclude wild birds and rodents and control insects from poultry facilities.

• Ensure disinfection of kennel or other facility where infected animals have been housed. Disinfectants include 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde, and iodine-based solutions.[3]

• Ensure proper biosafety procedures are followed in veterinary facility or farm (e.g., sterilization of instruments used on possibly infected animals, proper disposal of potentially infected tissue such as aborted placentas and fetuses), and that staff are aware of symptoms of infection.

• Quarantine infected animals. Ensure proper treatment of bulls if indicated.

• No animal vaccine is currently available for enteritis, but *C. fetus* bacterin can prevent abortions in sheep and genital campylobacteriosis in cattle.[4]

Agent

Campylobacter species are spiral, S-shaped, or curved, gram-negative rods (Figures 9-16, 9-17, and 9-18). More than 20 strains have been described, including *C. jejuni, C. coli, C. upsaliensis, C. larii, C. fetus,* and *C. helveticus.*[5] Most cases of *Campylobacter* enteritis in humans are believed to be due to *C. jejuni* or *C. coli*. However, when more sensitive isolation techniques are used, some cases have been found to be
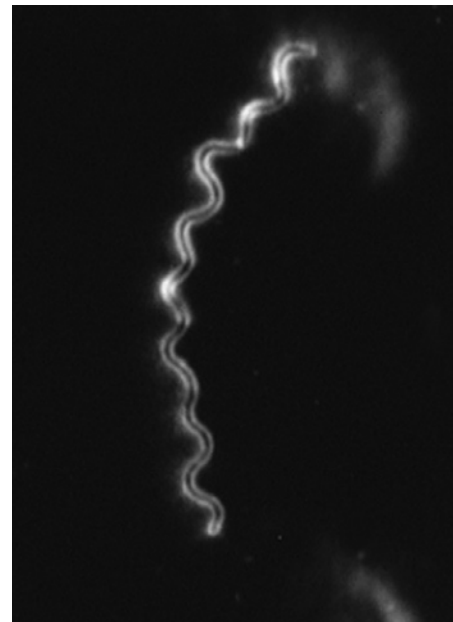
Figure 9-16 ■ *Campylobacter* species viewed by dark-field microscopy. Note the chaining of individual organisms, which are often mistaken for spirochetes. (From Songer JG, Post KW: *Veterinary microbiology: bacterial and fungal agents of animal disease*, St Louis, 2005, Saunders Elsevier. Courtesy J. Glenn Songer.)

Figure 9-17 ■ Electron micrograph of *Campylobacter.* (From Centers for Disease Control and Prevention, Atlanta, Ga.)

BOX 9-1 *CASE STUDY: CAMPYLOBACTER JEJUNI*

Campylobacter jejuni was diagnosed in a child by her physician. The child was exposed to a puppy that was mildly ill a few weeks previously and recovered fine. No specific diagnostic tests were performed on the puppy; it was treated symptomatically and recovered. The physician is concerned about the possibility of the puppy being the source of the *Campylobacter*. The puppy has had all routine dewormers and vaccinations and is in good health now.

Question/concern: The puppy is part of a much larger group of dogs and puppies (~100) that are currently being rehabilitated in foster homes. All were mixed together when they were removed from a common source environment several months ago. There have been no reports of diarrhea in other puppies or human household members among children or parents caring for the puppies over the past several months. Would a fecal culture now reveal *Campylobacter*? Would there be any value in screening other puppies, or should we just have *Campylobacter* on the differential and perform appropriate diagnostics should any other puppies become ill in the future?

Response: There have been several studies demonstrating the link of *Campylobacter* and illness in children. The population attributable risk is in the range of 5% to 7%. *Campylobacter* shedding is more frequent in kittens and puppies versus adult animals. At least in kittens, an average carriage of about 4 to 6 weeks was observed (unknown in dogs). Treatment for animals with diarrhea is appropriate because it likely decreases the days of shedding and the number of organisms shed. Appropriate hand hygiene is critical in households with foster puppies. Treatment for asymptomatic dogs would probably not be appropriate (because of antibiotic resistance issues) even though a fair number of puppies and kittens shed *Campylobacter* when they are asymptomatic. Likely the quantity of organisms is less, and studies seem to support contact with dogs with diarrhea as a source.[23]
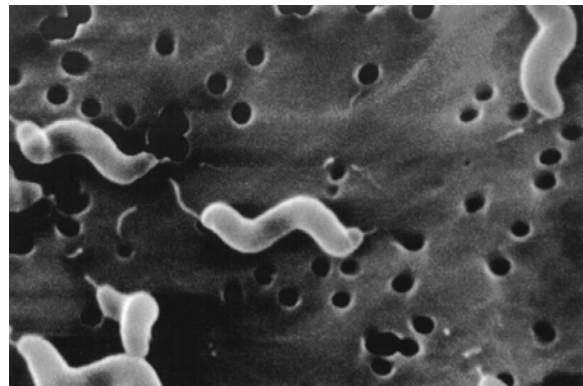
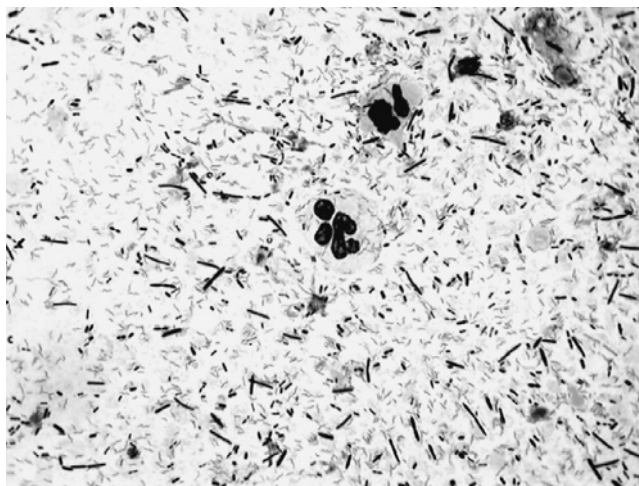**Figure 9-18** ■ *Campylobacter* species: canine fecal smear (Wright's stain, ×100). Fecal smear shows numerous *Campylobacter* species organisms (lighter-staining smaller bacteria), a mixed population of bacterial rods, and two degenerating neutrophils. The characteristic "gull wing" formations (visible on the surface of the neutrophil) are chains of three to five of these slender, gram-negative, comma-shaped, or curved motile rods. The organisms have the same morphologic characteristics in all species of animals. *Campylobacter* are often overlooked because of their small size. Animals can be carriers, in which case usually only very low numbers are seen. These organisms can be either the primary cause of diarrhea or act as secondary pathogens in conjunction with other enteric bacteria. *Campylobacter* species are difficult to culture. Neutrophils are not seen in normal stool and indicate an active infection. (From Quesenberry K, Carpenter JW: *Ferrets, rabbits and rodents: clinical medicine and surgery*, ed 2, St Louis, 2004, Saunders Elsevier.)

caused by *C. larii* and *C. fetus*. Fluoroquinolone-resistant *Campylobacter* infections are more likely to be severe with bloody diarrhea.

C. fetus is a gram-negative, motile bacteria. Based on current knowledge, it has distinctive epidemiological and clinical features. *C. fetus* has a tendency to invade the vascular endothelium[6] in humans and is an opportunistic pathogen causing mainly systemic infection. In animals, *Campylobacter fetus* subspecies *fetus (intestinalis)* is thought to be primarily an intestinal pathogen (although it has been associated with infertility[4]), whereas *C. fetus venerealis* infects the genital tract. Selective media used to culture other *Campylobacter* species use antibiotics that may inhibit *C. fetus*.[7] *C. fetus* also grows at a lower incubation temperature (25°C vs. 42°C) than other *Campylobacter* species.[8] Normal isolation techniques may not detect *C. fetus*, and as diagnostic methods improve, our understanding of *Campylobacter* infections will continue to evolve.

Geographical Occurrence

C. jejuni, *C. coli,* and *C. fetus* are found worldwide. In the developing world, *C. jejuni* and *C. coli* infections are considered to be mostly diseases of young people. The incidence of *C. fetus* in humans is uncommon but believed to be much higher than recorded.[8]

Groups at Risk

Because poultry flocks have high rates of colonization with *Campylobacter*, persons engaged in poultry raising and processing are at increased risk of infection.[10] Other risk factors

identified have been drinking unpasteurized milk, contact with farm animals, and eating poultry in restaurants.[11] *Campylobacter* is an important cause of travelers' diarrhea in travelers to countries with poor sanitation (Color Plate 9-8). Ownership of cats and dogs (especially puppies and kittens) is considered a risk factor for infection, although the extent of pet-to-human transmission remains unknown.[12]

Most human cases of *C. fetus* to date have occurred in immunocompromised persons, although cases in healthy individuals have been recorded.[13] Risk factors include hepatic cirrhosis, HIV infection, diabetes, and systemic lupus erythematosus.

Hosts, Reservoir Species, Vectors

C. jejuni and C. coli occur across a range of species and particular strains appear able to cross species barriers. Surveys of poultry, such as chickens and turkeys, have found colonization rates up to 100%, and contaminated chicken meat is considered a major source of infection for humans.

A survey of dogs and cats in Switzerland found colonization rates of 41% in dogs and 42% in cats.[14] A Taiwan survey reported higher rates in stray dogs versus nonstrays.[15]

C. fetus is widespread in cattle and sheep. It also occurs in reptiles. Unlike *C. jejuni*, it is not commonly recognized in poultry, and therefore poultry may not be a major source of human infection.[16]

Mode of Transmission and Life Cycle

C. jejuni and *C. coli* are transmitted by consumption of contaminated food, such as undercooked poultry or unpasteurized dairy products. It can also be transmitted by fecal-oral contact (Figure 9-19). Waterborne transmission is also possible.

The source of many human *C. fetus* infections is unknown, and the mechanism of transmission from animals to humans remains unclear.[8] In cattle, *C. fetus venerealis* is a sexually transmitted disease. However, cows and ewes may be chronically infected and may have colonization of the gallbladder, leading to fecal elimination. In sheep transmission is fecal-oral, with sexual transmission apparently not playing a role.[8]

Environmental Risk Factors

Environments contaminated by poultry manure, such as occurs in backyard poultry rearing, could propagate *C. jejuni* and *C. coli* infection. Because *Campylobacter* organisms can survive in water, the bacteria circulate in wild bird populations such as waterfowl and shorebirds.[17] Surface water can become contaminated with infected feces of wild and domestic birds; therefore pollution of water bodies is a potential source of infection.

Transmission of *C. fetus* in sheep and cows is thought to involve environmental contamination of grazing areas by infected tissues and feces.[8]

Disease in Humans

Campylobacter enteritis in humans is an acute but usually self-limited diarrheal illness characterized by abdominal cramping, diarrhea, and fever. The incidence is higher among infants and young adults ages 15 to 44 years.
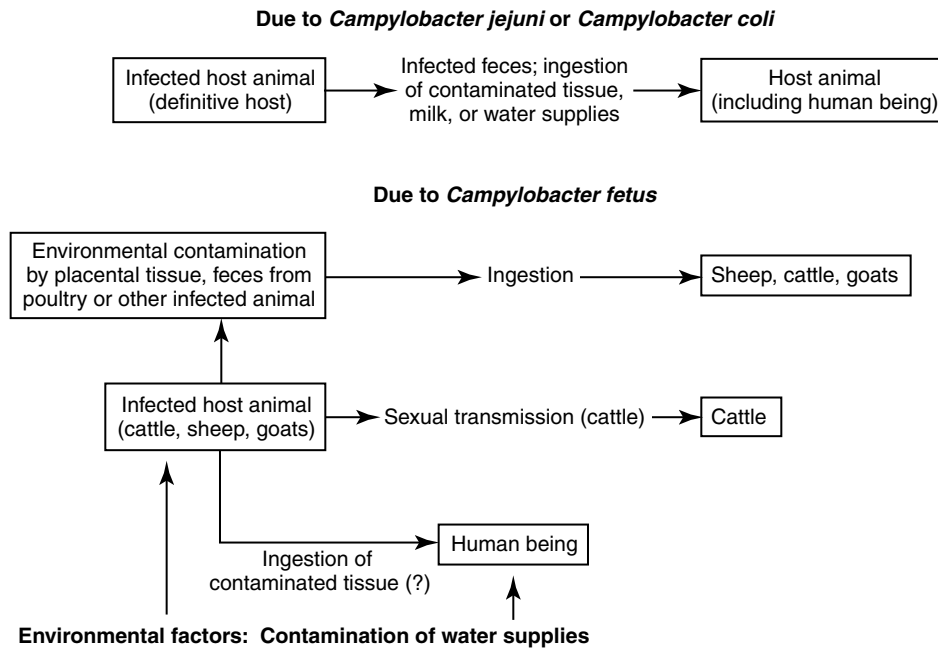
Due to *Campylobacter jejuni* or *Campylobacter coli*

```
┌─────────────────────┐   Infected feces; ingestion   ┌─────────────────────┐
│ Infected host animal │──── of contaminated tissue, ──▶│     Host animal      │
│   (definitive host)  │      milk, or water supplies  │(including human being)│
└─────────────────────┘                                └─────────────────────┘
```

Due to *Campylobacter fetus*

```
┌──────────────────────────┐                          ┌──────────────────┐
│Environmental contamination│                          │                  │
│ by placental tissue, feces│──── Ingestion ──────────▶│ Sheep, cattle,   │
│   from poultry or other   │                          │     goats        │
│      infected animal      │                          └──────────────────┘
└──────────────────────────┘
           ▲
┌──────────────────────┐                               ┌────────┐
│ Infected host animal │──── Sexual transmission ─────▶│ Cattle │
│ (cattle, sheep, goats)│        (cattle)              └────────┘
└──────────────────────┘
    ▲         │
    │         ▼
    │    ┌──────────────┐
    │    │ Human being  │
    │    └──────────────┘
 Ingestion of                  ▲
 contaminated tissue (?)
```

Environmental factors: Contamination of water supplies

Figure 9-19 ▪ Life cycle, campylobacteriosis.

In many cases, blood or mucus is noted in the feces, indicating colorectal inflammation.[18] The abdominal pain may mimic appendicitis. Usually the diarrhea resolves after several days without specific treatment, but other symptoms may persist longer.

Bacteremia and other extraintestinal manifestations are rare, but complications of infection may include erythema nodosum, uveitis, meningitis, and reactive arthritis. Guillain-Barré syndrome occurs in approximately 1 of 1000 cases of *C. jejuni* infection.[19]

C. fetus is an opportunistic pathogen in humans typically presenting as an acute or chronic bacteremia or thrombophlebitis. Complications include myocarditis, endocarditis, meningitis, and abortion (Figure 9-20).

Disease in Animals

Campylobacter may be present in animals without signs or it may cause diarrhea. Adult animals and poultry older than 1 week are usually subclinical carriers.[3,18,19] The diarrhea is usually most severe in young animals (e.g., in puppies and kittens from birth to 6 months) or in debilitated animals.[4,20] The diarrhea can range from watery to mucus with blood or bile streaking. Affected animals may have reduced appetite and, rarely, vomiting. Tenesmus is common. Diarrhea also occurs after infection in cattle (especially calves), primates, ferrets, and mink.[4] In sheep, *C. jejuni* infection is associated with abortion (Color Plate 9-9).[21]

C. fetus is an important cause of infertility and abortions in cattle and sheep. In cattle, bovine genital campylobacteriosis presents with early fetal death, infertility, and abortion.[4]

Table 9-12 shows comparative clinical presentations of campylobacteriosis in humans and other animals.

Diagnosis

Diagnosis in humans is based on culturing the organism from feces, blood, bone marrow, or other tissue using correct media and incubation procedures. It should be recognized that the selective media may inhibit the growth of certain *Campylobacter* species such as *C. fetus*, leading to false-negative results. Identification of organisms in feces using phase-contrast or dark-field microscopy can be used to make a presumptive diagnosis.[5] PCR techniques have recently been developed and may play a greater role in diagnosis in the future.

In animals, cultures and microscopic examination of feces or reproductive discharges are also used. Agglutination and ELISA tests are used on vaginal mucus of cows suspected to be infected.

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Figure 9-20 ▪ Human cardiac abscess from *C. fetus* bacteremia. *AB*, Abcess; *RA*, right atrium; *RV*, right ventricle; *TV*, tricuspid valve. (From Peetermans WE, De Man F, Moerman P et al: Fatal prosthetic valve endocarditis due to *Campylobacter fetus, J Infect Dis* 41(2):180, 2000.)

Table 9-12 ■ Campylobacteriosis: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans *(Campylobacter jejuni, C. coli)*	Infants and young adults; travelers to developing countries; ingestion of contaminated meat, unpasteurized dairy products; occupational exposure to animal feces, exposure to sick or colonized pet	2-5 days[18]	Diarrhea, often with mucus or blood, abdominal cramping, fever	Fecal leukocytes, organisms seen on Gram stain, dark-field or phase-contrast microscopy of feces, fecal culture
C. fetus	Immunocompromised, diabetes, cirrhosis infection, SLE, cancer	3-5 days	Gastrointestinal symptoms, bacteremia, endocarditis	Blood culture
Dogs, cats, cattle, sheep, chickens, turkeys, mink, ferrets, pigs, nonhuman primates, others *(C. jejuni, C. coli)*	Ingestion of contaminated food or water Young animals, stressed or debilitated animals at increased risk	3 days[4]	Diarrhea, usually mild, may have mucus or blood; loss of appetite, occasional vomiting, and fever[8] In sheep, abortion near end of pregnancy, stillbirth[16] Mastitis in cattle	CBC may show leukocytosis Fecal leukocytes, organisms seen on Gram stain or phase-contrast microscopy of stool, fecal culture
Sheep *(C. fetus)*	Ingestion of infected material	7-25 days	Abortion near end of pregnancy, stillbirth[8]	Dark-field and phase-contrast microscopy of placenta, fetal abomasums, and uterine discharge[3]
Cattle *(C. fetus)*	Ingestion of infected material, sexual transmission		Subclinical carriage Endometritis, embryonic death, prolonged estrous cycles, abortions	Vaginal mucus agglutination test, ELISA test of vaginal mucus

CBC, Complete blood cell count; *SLE*, systemic lupus erythematosus.

Treatment

Treatment in Humans

Most human enteritis cases are self-limited and resolve with only supportive therapy such as replacement of fluid and electrolytes, lactose-free diet, and avoidance of caffeine. Antibiotic treatment is reserved for more severe cases, including six or more unformed stools per day, and/or temperature of 101.5° F or more, and significant persistent tenesmus, stool blood, and leukocytes. Immunocompromised patients (e.g., individuals who are HIV positive) should be treated with antibiotics to prevent systemic complications[18] Treatment in humans is outlined in Table 9-13. Although in the past ciprofloxacin has been used as a primary therapeutic agent, high rates of resistance to fluoroquinolones have been observed in certain settings.[22]

Treatment in Animals

As in humans, many enteritis cases in dogs and cats are self-limited. When signs are severe (e.g., high fever or dehydration), persist beyond 5 days, or are present in immunocompromised patients, treatment with antibiotics is recommended.

Table 9-13 ■ Campylobacteriosis Treatment in Humans and Other Animals

Species	Primary Treatment	Alternative
Humans (adults) *(Campylobacter jejuni)*	Azithromycin mg PO q24h x 3 days	Erythromycin stearate 500 mg PO qid x 5 days
(C. fetus)	Gentamicin	Ampicillin, chloramphenicol, erythromycin[9]
Dog and cat *(C. jejuni, C. coli)*	Erythromycin 10-20 mg/kg PO q8h × 5 days	Tylosin 11 mg/kg PO q8h × 7 days *or* neomycin 10-20 mg/kg PO q8h × 5 days[13]
Bull *(C. fetus)*	Streptomycin 20 mg/kg SC, 1-2 treatments, streptomycin in oil-based suspension applied to the penis × 3 days	Tylosin 11 mg/kg PO q8h × 7 days *or* neomycin 10-20 mg/kg PO q8h × 5 days

Erythromycin is the drug of choice.[20] Antibiotics may prevent abortions in sheep or prevent the spread of genital campylobacteriosis by treating infected bulls.[3] Good hygiene is critical for prevention. In cattle herds, antibiotic treatment is not considered practical.[4]

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CHLAMYDOPHILA PSITTACI AND RELATED INFECTIONS

Peter M. Rabinowitz and Lisa A. Conti

Chlamydophila psittaci *and related infections (ICD-10 A70 Psittacosis; ICD-10 A74 Other diseases caused by chlamydiae)*

Other names in humans: psittacosis, ornithosis, chlamydiosis, parrot fever

Other names in animals: avian chlamydiosis; mammalian chlamydiosis, chlamydial conjunctivitis, feline chlamydial pneumonitis, septic abortion of sheep and goats

Chlamydophila (formerly *Chlamydia*) *psittaci* infection from exposure to birds causes disease in humans ranging from mild flulike signs to severe pneumonia and sepsis. Although fewer than 50 human cases of psittacosis are reported yearly in the United States,[1] it is likely that many cases go undetected. *C. psittaci* commonly infects psittacine (parrot family) birds that are used as pets, but domestic poultry flocks, especially turkeys and ducks, can develop widespread infection with significant flock mortality and occupational risk to poultry workers. Human disease with mammalian chlamydiae (i.e., *C. abortus*, *C. felis*, and *C. pneumoniae*) is rarely reported. The diagnosis of chlamydiosis can be challenging in humans and other animals.

New molecular evidence is broadening our understanding of the host range and clinical spectrum of *Chlamydophila* infections.[2] Therefore clinicians should maintain a high index of suspicion in the appropriate settings where infection can occur.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Characterize the risk in the community related to pet shops, aviaries, bird ownership, and poultry production.
- Become familiar with the National Association of State Public Health Veterinarians *Compendium of Measures to Control* Chlamydophila psittaci *Infection Among Human Beings (Psittacosis) and Pet Birds (Avian Chlamydiosis).*[3] These measures are summarized in Box 9-2.
- Conduct an investigation of human cases, including surveillance of pet shops and poultry farms, to detect sources of infection and other human cases. If infected birds are found, ensure that they are treated or destroyed and the area is decontaminated with a disinfectant.[4]

BOX 9-2   *MEASURES FOR PSITTACOSIS PREVENTION*

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Adapted from *Compendium of measures to control* Chlamydophila psittaci *infection among human beings (psittacosis) and pet birds (avian chlamydiosis),* 2008, National Association of State Public Health Veterinarians.

- Coordinate with agriculture officials to control the disease in bird populations.
- Ensure that poultry workers with occupational risk for *C. psittaci* infection are informed about the disease and its prevention through exposure controls and protective equipment.

Human Health Clinicians

- Consider the diagnosis in all patients with bird contact (avian chlamydiosis) who present with respiratory symptoms or fever, as well as patients with keratoconjunctivitis (or rarely endocarditis and glomerulonephritis) and cat contact (mammalian chlamydiosis).
- Report suspected cases to public health authorities. See CDC case definition: http://www.cdc.gov/ncphi/disss/nndss/casedef/psittacosiscurrent.htm.
- Counsel patients with psittacine birds to take steps to protect their birds from exposure to *C. psittaci* and to seek veterinary care for ill birds, especially if owners are immunocompromised. Other risk reduction measures include avoiding mouth-to-beak contact and appropriate personal protective equipment (PPE) when cleaning cages or handling dead birds (see Box 9-2).
- If caring for workers with occupational exposure to birds (e.g., pet shop workers, poultry workers), ensure that they immediately report symptoms of fever, myalgias, and cough, and that the workplace is adopting preventive practices (see Box 9-2), including respiratory protection for workers who are working with ill or potentially exposed birds.
- Counsel pregnant patients to avoid contact with pregnant or aborting sheep and goats.

Veterinary Clinicians

- Counsel bird owners on the signs of psittacosis, how to protect their birds from exposure, and how to reduce risks to humans, especially if owners are immunocompromised.
- Consider the diagnosis of chlamydiosis in any sick bird with lethargy and nonspecific signs, especially if recently purchased or stressed (e.g., transported).
- Follow local and state reporting regulations; contact local health department or Department of Agriculture.
- Train veterinary personnel in biosafety measures, such as wearing masks and gloves when working with potentially infected birds, and use of strict personal hygiene (e.g., handwashing and cleaning/disinfecting footwear) to prevent spreading the organism to other animals.
- If a case is diagnosed in a cat, immunize cats in the household or cattery using *C. psittaci* vaccine. A live *C. abortus* vaccine may reduce shedding in sheep.

Agent

C. psittaci is an intracellular bacterium closely related to the human pathogen *Chlamydia trachomatis* (causes venereal infection in humans) and other zoonotic Chlamydiae (Table 9-14). A number of different strains (serovars) of *C. psittaci* have been described; the majority are avian pathogens. The strains vary in virulence and zoonotic potential; for example, the turkey strain may be more virulent than serovars that affect pigeons and ducks.[5] Mammalian strains of zoonotic Chlamydiaceae are *Chlamydophila felis*

Table 9-14 ▪ Comparison of Classification of *Chlamydophila* and *Chlamydia*

Hosts	Preferential Tissues	Before 1999	After 1999
Chlamydophila			
Birds	Genital, lung, internal organs	*Chlamydia psittaci*	*psittaci*
Cattle, sheep	Brain, eye, joints	*Chlamydia pecorum*	*pecorum*
Humans, koalas, horses	Lung, joints, endothelial	*Chlamydia pneumoniae*	*pneumoniae*
Sheep, mammals	Intestines, placenta	*Chlamydia psittaci*	*abortus*
Guinea pigs	Bladder, eye, spleen	*Chlamydia psittaci*	*caviae*
Cats	Eye, genital, joints, lungs	*Chlamydia psittaci*	*felis*
Chlamydia			
Humans	Ocular and urogenital, neonatal lung	*Chlamydia trachomatis*	*trachomatis*
Rodents	Many internal organs	*Chlamydia trachomatis*	*muridarum*
Swine	Eye, intestines, lung	Novel species	*suis*

Adapted from Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier.

(formerly *Chlamydia psittaci*, feline strain, causes conjunctivitis in cats), *C. abortus* (formerly *Chlamydia psittaci*, mammalian abortion strain or serotype 1, causes abortion in ruminants, especially sheep and goats), and *C. pneumoniae* (formerly *Chlamydia pneumoniae*, previously considered a human pathogen, but has been isolated from horses, reptiles, and amphibians).[6]

The CDC considers *C. psittaci* a category B biological warfare agent because of its ability to be produced and disseminated in quantities sufficient to affect large populations.[7]

Geographical Occurrence

Worldwide.

Groups at Risk

Groups at increased risk for *C. psittaci* infection include owners of birds, pet store workers, veterinarians, zookeepers, live poultry and poultry processing workers, and diagnostic laboratorians. Recent studies have found seroprevalence rates as high as 15% in workers at pet bird breeding facilities.[8]

Seroprevalence rates of 15% have been reported in livestock farmers.[9] Pregnant women have developed severe infection with *C. abortus*, including sepsis, stillbirth, and abortion after contact with birth products of sheep and goats, but such cases are considered rare.[10]

Hosts, Reservoir Species, Vectors

C. psittaci occurs in most birds. One serovar is found in a wide range of psittacine birds, including parrots, parakeets, and cockatiels (Color Plate 9-10). Another infects turkeys and ducks and, rarely, chickens. Certain Chlamydiae infect mammals, and a high rate of subclinical carriage has been reported in rodents.[11] Prevalence rates of 5% to 10% in cats have been reported, and exposure to infected cats has been linked to human infection.[12]

Many animals shed the organisms in the absence of clinical signs. Crowding and other stressors appear to increase the rate of fulminant diseases in birds. Wildlife may serve as a reservoir and pose an infectious threat to domestic poultry.[5]

Mode of Transmission and Life Cycle

Chlamydiae exists in two forms, an infectious but metabolically inactive elementary body that is relatively stable in the environment, and the metabolically active but noninfectious reticulate body (Figure 9-21).[5] Infection is initiated by the elementary body attaching to susceptible cell membranes, primarily in the respiratory and later gastrointestinal tracts.[13] Transformation of the elementary body to the reticulate body occurs within several hours, after which the reticulate body creates progeny that differentiate into elementary bodies and are released from infected cells. The bacteria can be shed in the feces, leading to fecal-oral transmission[5]; in addition, nasal, ocular, and uterine discharges can lead to direct inoculation into mucous membranes or aerosol transmission.

Bird species implicated in zoonotic aerosol transmission include psittacine birds, poultry, shorebirds, and raptors.[3] Direct handling of an infected bird or cat followed by self-inoculation of conjunctiva or other mucous membranes is another potential route of animal-human transmission, as is beak-to-mouth contact (kissing a pet bird). Person-to-person transmission has been reported in close contacts of infected persons.[14]

Environmental Risk Factors

Under certain conditions, the bacterial elementary body can persist for prolonged periods in the environment. This can lead to reinfection of poultry flocks or pet birds through both oral and respiratory routes.

Disease in Humans

C. psittaci can cause an acute febrile syndrome with headache, myalgias, cough, and photophobia. Respiratory symptoms may be mild in relation to the chest x-ray findings, which may appear worse than the patient's condi-
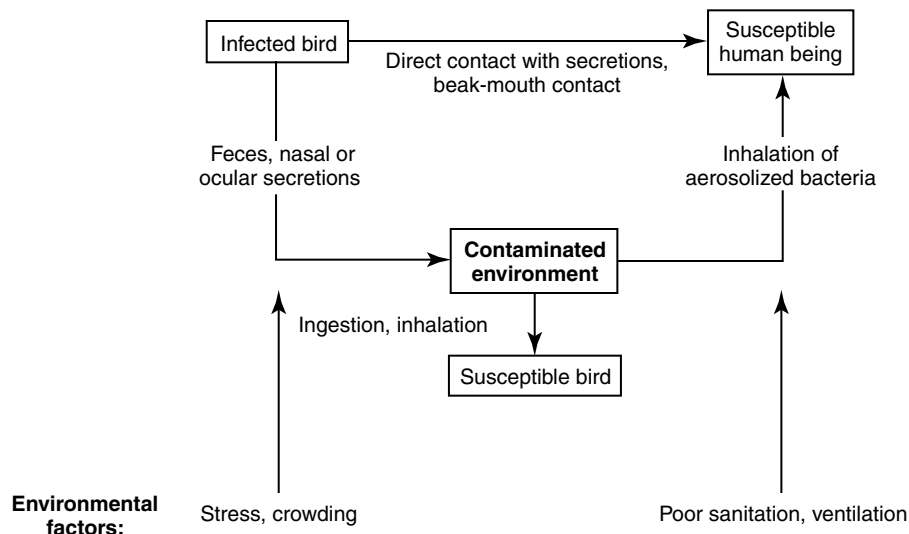
Figure 9-21 ■ Life cycle, *Chlamydophila psittaci* infection.

tion appears (Figure 9-22). Sputum production is often scant. Hepatomegaly and pharyngeal erythema often occur. The pulse may be paradoxically slow in relation to the degree of fever. Skin signs include Horder's spots, a pink, blanching maculopapular rash.[15] Keratoconjunctivitis has been reported in cases of contact with infected cats.[15] Complications of infection include hepatitis, splenomegaly, hemolytic anemia, disseminated intravascular coagulation (DIC), endocarditis, myocarditis, pericarditis, and glomerulonephritis. Neurological complications including hearing loss, cranial nerve palsy, cerebellar symptoms, and confusion can also occur.

In more severe cases, progressive pneumonia and acute respiratory distress syndrome (ARDS) develop with multiorgan failure. Infection in pregnancy can cause severe complications including DIC and fetal death. Past infection does not appear to confer subsequent immunity.[15]
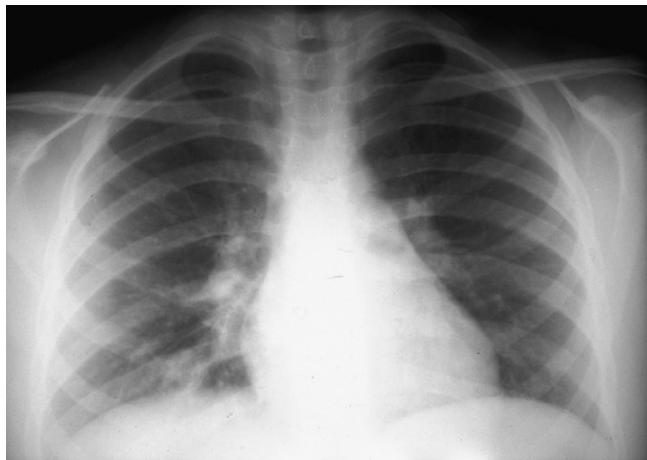
Figure 9-22 ■ Chest radiograph of a 9-year-old girl with a 2-week history of fever, headache, and hacking cough. She was the caretaker of the family's cockatoo. Serum complement fixation antibody titer for *C. psittaci* was 1:256. (From Long SS, Pickering LK, Prober CG (eds): *Principles and practice of pediatric infectious diseases*, ed 3, Philadelphia, 2008, Saunders Elsevier. Courtesy of S.S. Long.)

Many aspects of the disease remain incompletely understood, including an association with ocular adnexal lymphoma, and indolent lymphoma from chronic avian chlamydiosis.[10,16,17] These associations, if true, may lead to preventive therapies for these lymphomas.

Severe complications including sepsis, stillbirth, and miscarriage can develop in pregnant women infected with *C. abortus* from contact with pregnant sheep and goats.[18] The role of other Chlamydiae and *Chlamydia*-like organisms in obstetrical pathology is emerging.[19]

Disease in Animals

Many birds and mammals shed Chlamydiae without any signs. However, *C. psittaci* can cause morbidity and mortality in psittacine birds, with malaise, weight loss, diarrhea, and conjunctivitis. Stress and crowding appear to increase the prevalence of clinical disease.[5] As in humans, previously infected animals may become reinfected.

Cats typically develop conjunctivitis and mild upper respiratory disease. Conjunctivitis may also be seen in other species (Figures 9-23 and 9-24). Kittens 2 to 6 months old are more likely to be infected. *C. abortus* is a major cause of reproductive failure and abortion in sheep and goats. Chlamydial infection has been associated with horses with recurrent airway obstruction.[20] Table 9-15 provides clinical presentations of chlamydiae infections in humans and other animals.

Diagnosis

The differential diagnosis in humans includes other causes of atypical pneumonia, including *Legionella*, *Mycoplasma*, *C. pneumoniae*, *Coxiella*, and influenza. The clinical presentation of an atypical pneumonia in the setting of a history of exposure to birds should lead clinicians to strongly consider the diagnosis of psittacosis.

Confirmation of the diagnosis is usually by serology, using either complement fixation or microimmunofluorescence (MIF). Serology specimens should be obtained acutely and
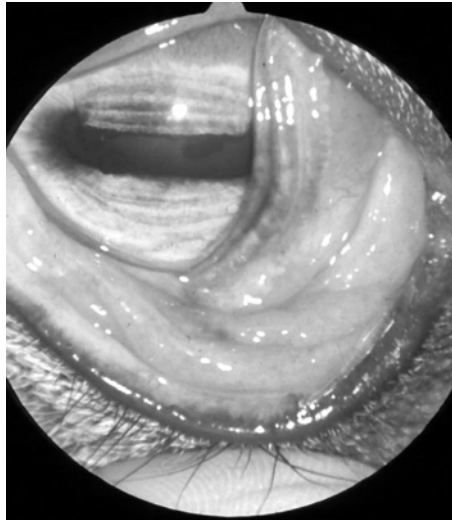
Figure 9-23 ▪ Acute *Chlamydia* species conjunctivitis in a heifer. (From Fubini S: *Farm animal surgery*, Philadelphia, 2004, Saunders Elsevier.)

Figure 9-24 ▪ Severe conjunctivitis and periocular edema in a Morelet's crocodile *(Crocodylus moreletii)*. (From Bewig M: *Manual of exotic pet practice*, St Louis, 2009, Saunders Elsevier.)

2 to 3 weeks later. Because antibiotics may blunt the antibody response, a third set of serologic tests may be obtained 4 to 6 weeks after the acute sample if the results of the second set are equivocal.

CDC surveillance criteria for a confirmed case of psittacosis are as follows:

- Isolation of *C. psittaci* from respiratory secretions, *or*
- Fourfold or greater increase in antibody against *C. psittaci* by complement fixation or MIF to a reciprocal titer of ≥32 between paired acute- and convalescent-phase serum specimens, *or*

- Presence of immunoglobulin M antibody against *C. psittaci* by MIF to a reciprocal titer of ≥16.[21]

Culture of the organism is difficult and poses a risk to laboratory personnel and therefore should be performed only in qualified laboratories. A PCR test is available through the CDC.

In birds, the diagnosis can be challenging, especially in asymptomatic cases. A combination of culture, antibody testing, and antigen detection is recommended.

For necropsy diagnosis, tissue specimens from the liver and spleen are preferred. In live birds, conjunctival, choanal,

Table 9-15 ▪ Chlamydiae Infections: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans	Contact with sick birds and their environment	5-15 days[15]	Headache, fever, myalgias, cough, photophobia, scant sputum, shortness of breath; rarely endocarditis, hepatitis, neurological complications	Pulmonary infiltrates on x-ray, elevated WBC, erythrocyte sedimentation rate, serology (CF, IFA), PCR, culture
	Contact with cats experiencing keratoconjunctivitis		Conjunctivitis (exposure to *C. felis*)	PCR (may not distinguish species), culture
	Pregnant women working with sheep and goats		Miscarriage (exposure to *C. abortus*)	
Birds	Crowding, other stressors	3 days to weeks Latent infections possible	Often subclinical Lethargy, diarrhea, malaise, conjunctivitis, ruffled feathers, ocular or nasal discharge	Culture and serology (IFA, ELISA) Antigen, PCR
Cats	Crowding	3-10 days[12]	Often subclinical Chronic conjunctivitis, photophobia, pneumonitis, sneezing	Culture, serology, IFA
Sheep, goats	Parturition	Months	May be subclinical Spontaneous abortion	Culture, serology

CF, Complement fixation; *WBC*, white blood cell count.

and cloacal swab specimens or liver biopsy specimens can be used. Fecal specimens can be collected over several days and pooled for increased sensitivity. As with diagnosis of human disease, the culture of *C. psittaci* requires specialized laboratory facilities to minimize risk to laboratory personnel. Conjunctival scrapings of various animals may reveal elementary bodies in epithelial cells (Figure 9-25).

Serological tests available include elementary body agglutination (EBA) for detection of IgM antibodies, and indirect fluorescent antibody test (IFA) to detect IgG antibodies.

Complement fixation (CF) is more sensitive than agglutination methods. Antigen tests include ELISA tests that were originally developed for identification of *Chlamydia trachomatis* in humans and IFAs to detect antigen. PCR is available in a number of diagnostic laboratories to detect C. *psittaci* DNA in samples. Care is necessary in the preparation of samples for PCR testing to prevent environmental contamination.[3]
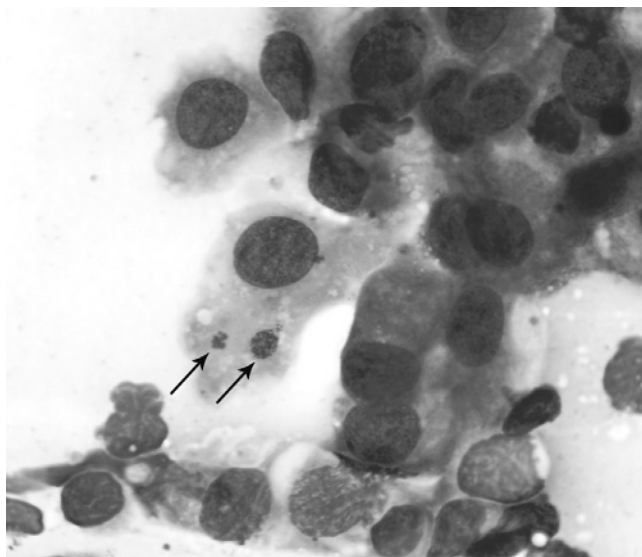
Figure 9-25 ■ Conjunctival scraping from a cat with chlamydial conjunctivitis. Elementary bodies of *Chlamydophila felis* are found in an epithelial cell *(arrows)*. (Wright's stain, original magnification ×1000.) (From Young KM, Taylor J: Laboratory medicine: yesterday, today, tomorrow: eye on the cytoplasm, *Vet Clin Pathol* 35:141, 2006.)

Treatment

Treatment in humans depends on whether the diagnosis is suspected or confirmed. If the diagnosis is not certain, the patient should receive antibiotics to cover the spectrum of organisms causing community-acquired pneumonia, with the regimen adjusted to the severity of disease and existing comorbid conditions such as alcoholism or chronic obstructive lung disease. Once the diagnosis is confirmed, more specific therapy can be given as outlined in Table 9-16. Doxycyline and tetracycline are the mainstay of treatment in humans but are contraindicated in children younger than 8 years and pregnant women, for whom a macrolide antibiotic such as erythromycin may be considered. However, erythromycin may be less efficacious in severe cases and it may not protect the fetus of a pregnant patient.[15]

Treatment in animals also relies on antibiotics of the tetracycline class. Euthanasia may be considered as a control measure during outbreaks. In cats, a vaccine is available that does not prevent disease but may reduce the severity and duration of illness.[12]

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Table 9-16 ■ Treatment of *Chlamydophila Psittaci* Infection in Humans and Other Animals		
Species	**Primary Treatment**	**Alternative Treatment**
Humans: adult	Doxycycline 100 mg PO or IV q12h × 10-21 days[22]	Tetracycline 500 mg PO q6h × 10-21 days[22]
<8 yr, pregnancy	Doxycycline, tetracycline contraindicated; consider macrolide (erythromycin), specialist consultation	
Birds	Doxycycline 25-50 mg/kg q24h PO for 30-45 days (dose and time are species dependent)	1% Chlortetracycline in medicated feed; some injectable doxycyclines (consult with avian veterinarian)
Cats	Doxycycline 5 mg/kg PO q12h × 3-4 wk Ophthalmic ointments containing tetracycline q8h	Tetracycline 22 mg/kg PO q8h × 3-4 wk[22] (may affect growing teeth of young kittens)
Sheep, goats	Long-acting oxytetracycline 20 mg/kg, with a second injection 3 weeks later	Tetracycline[21]

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CRYPTOSPORIDIOSIS

Peter M. Rabinowitz and Lisa A. Conti

Cryptosporidiosis (ICD-10 A07.2)

Like *Giardia, Cryptosporidium* species are a common parasitic cause of infectious diarrhea in humans and are found in many vertebrate species. Many episodes of infection are mild enough that they do not come to medical attention. Yet because of its capability to cause massive human outbreaks through waterborne exposure, it is considered a category B bioterrorism agent. In immunocompromised patients, cryptosporidiosis can cause serious and even fatal disease. A growing body of knowledge supports the importance of cross-species transmission between animals, especially calves, and humans.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Be familiar with CDC guidelines: "Cryptosporidiosis Outbreak and Response Evaluation."[1]
- Analyze and report trends from compulsory reports of human disease.
- In the event of a case report, determine risk factors for infection and conduct additional case finding.
- Public health laboratories should determine the genotype to assist with source tracking.
- Consider zoonotic sources of infection (farm animals/petting zoos, water supplies with animal contact) in addition to human-to-human spread (especially in day care settings).
- Educate the public, veterinarians, and human health clinicians about risk factors for transmission. Highlight the need for strict hygiene measures for, or restrictions on, petting zoos and other animal settings (see the National Association of State Public Health Veterinarians *Compendium of Measures to Prevent Disease Associated with Animals in Public Settings,* 2009; http://www.nasphv.org/Documents/AnimalsInPublicSettings.pdf).
- Disinfect the environment of oocysts using 5% ammonia solution.[2] Recognize the limited efficacy of disinfection procedures and place emphasis on thorough cleaning.
- Provide preventive guidance for day care facilities, recreational water facilities, and boil water notification. Remove reservoirs (recently infected people) from contact with susceptible populations. Exclude children with diarrhea from school or child care centers, water parks, swimming pools, and so on.
- Support policies to keep public areas free of animal feces.
- Consider efficacy of local water treatment procedures with regard to removal of oocysts (i.e., chlorination lacks efficacy; therefore alternative disinfection procedures such as filtration or ozonation may be required).

Human Health Clinicians

- Report cases to public health authorities: http://www.cdc.gov/mmwr/preview/mmwrhtml/00047449.htm.
- Include questions about animal contact for every patient presenting with diarrhea.
- Consider occupational exposure of cattle workers and animal shelter workers.
- Person-to-person transmission is possible; counsel infected persons about hand hygiene and avoiding fecal exposure during sexual activity.

Veterinary Clinicians

- Counsel owners and any others in contact with infected animals about the zoonotic risk, need for hand hygiene after handling pet, feces, pet toys, and other objects that are potentially infected with cysts.

- Decontaminate infected animal's coat with shampoo and kennels or other environments with an 18-hour exposure to 5% ammonia, 10% formol saline, or 3% hydrogen peroxide.[2]
- Counsel persons who work with young ruminants or animal shelters of the increased potential for exposure and provide a clean birthing environment. Neonates should receive colostrum, segregate calves from other calves for the first 2 weeks of life, and maintain hygienic husbandry practices including fly and rodent control.
- Counsel immunosuppressed persons regarding the risks of animal exposures.

Agent

Cryptosporidia are protozoan parasites of the coccidia group in the phylum Apicomplexa (Figure 9-26). At least 30 species of *Cryptosporidium* and multiple genotype variations have been described in a wide number of animal species (Table 9-17). The two species believed to cause most cases of human infections are *C. hominis* (formerly known as *C. parvum* anthroponotic genotype or genotype 1) and *C. parvum*. *C. hominis* is a human pathogen, although infection has
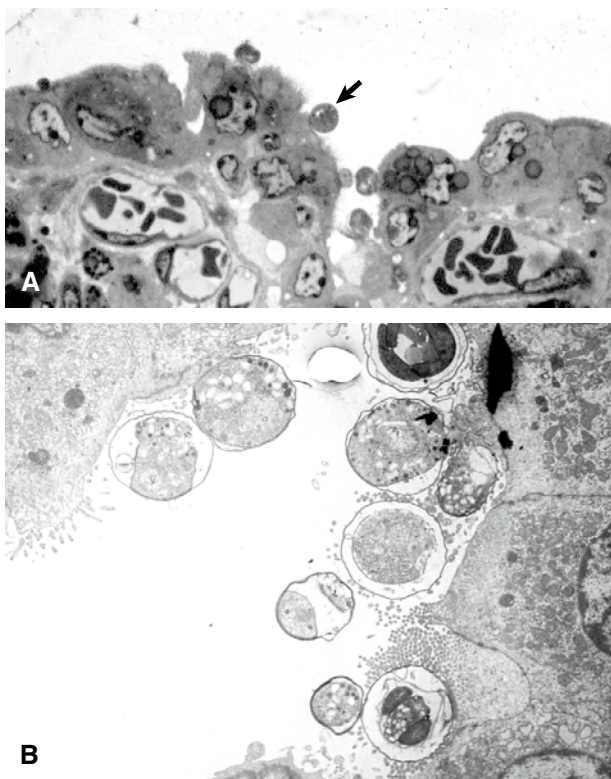
Figure 9-26 ■ Cryptosporidiosis, small intestine. **A,** Cow. Cryptosporidia *(arrow)* are attached to the microvillus border of the enterocyte membrane. Plastic-embedded, toluidine blue–stained section. **B,** Rabbit. The Cryptosporidia form a trilaminated enveloping membrane upon fusion with the enterocyte membrane. Their location is thus intracellular, but extracytoplasmic. Microvilli are effaced. Transmission electron micrograph, uranyl acetate and lead citrate stain. (From McGavin MD: *Pathologic basis of veterinary disease*, ed 4, St Louis, 2006, Mosby Elsevier. *A,* Courtesy Dr. A.R. Doster, University of Nebraska; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. *B,* Courtesy Dr. H. Gelberg, College of Veterinary Medicine, Oregon State University.)

Table 9-17 ■ *Cryptosporidium* Species Infecting Humans and Other Animals

Host	Major Species	Minor Species
Humans	*C. hominis, C. parvum*	*C. meleagridis, C. felis, C. canis, C. suis, C. baileyi,* cervine genotype
Cats	*C. felis*	
Cattle	*C. parvum, C. bovis, C. andersoni* deer-like genotype	*C. suis*
Chickens	*C. baileyi*	*C. meleagridis, C. galli*
Deer	*C. parvum,* deer genotype	
Dogs	*C. canis*	
Horses	Horse genotype	
Lizards	*C. serpentis, C. varanii*	Lizard genotype
Mice	*C. muris,* mouse genotype	
Sheep	Cervine genotypes 1-3, bovine genotype	
Snakes	*C. serpentis*	*C. varanii,* snake genotype
Squirrel	*C. muris,* squirrel genotype	
Swine	*C. suis*	Pig genotype II
Turkey	*C. meleagridis, C. baileyi*	

Adapted from Fayer R, Xiao L: *Cryptosporidium and cryptosporidiosis*, Boca Raton, FL, 2007, CRC Press, p 11.

been found in lambs, cattle, and other mammals. *C. parvum* infects humans, cattle, and other ruminants. Other species reported in humans include *C. canis* (dogs), *C. felis* (cats), and *C. meleagridis* (birds).

Cryptosporidia colonize the intestinal and biliary tracts but can also be found in the lungs. The organism reproduces in the intestinal tract to produce oocysts. Oocysts are immediately infectious as shed in feces. The oocysts measure 2.5 to 5 microns in diameter and can survive in moist environments, including water supplies, for several months. They are resistant to chlorination but are inactivated by boiling water or ozonation.

Geographical Occurrence

C. parvum occurs worldwide in animals and humans. Human prevalence is greater in developing countries with poor sanitation practices. Reported rates of infection in human populations range from 20% in developing countries to 1% to 4% in developed countries.[3]

Groups at Risk

Children younger than 2 years, their caregivers, and immunocompromised persons have an increased risk of infection. Other risk groups include animal handlers, travelers, contacts of infected persons, and men who have sex with men.

Hosts, Reservoir Species, Vectors

Humans are the reservoir for *C. hominis*, whereas humans, cattle, and other ruminants (e.g., goats, sheep, deer, elk) appear to be major reservoirs for *C. parvum*.[4] *C. muris* infects mice and cattle gastric glands, and chickens are the reservoir for *C. baileyi*. In many individuals and species, asymptomatic carriage may occur with the ability to transmit the infection to others and the environment. The zoonotic potential of avian Cryptosporidia has not been fully elucidated.

Mode of Transmission and Life Cycle

Each oocyst contains four sporozoites that are the infective phase of the parasite (Figure 9-27). When shed in feces, the oocysts are immediately infective. Upon ingestion by a host,

the sporozoites are released and invade the mucosa of the intestinal tract. Sporozoites mature into trophozoites that multiply asexually first. Then these trophozoites undergo sexual reproduction (meronts) to produce sporozoites, most of which acquire a protective cover to form an oocyst. These oocysts are passed in the feces, where they are immediately infective. Sporozoites that remain in the intestine without developing a cyst wall are able to reinfect the host, perpetuating infection.[5] The infectious dose is about 130 organisms to initiate a *C. parvum* infection in 50% of healthy volunteers.[6] Cattle can shed up to 1 million organisms per gram of feces.

Most transmission appears to occur through ingestion of oocysts. Vehicles of transmission include drinking water, direct fecal-oral contamination, foodborne exposure, or contact with contaminated objects leading to ingestion (Figure 9-28). Infected drinking water and freshwater bathing areas have been the sources of large human outbreaks, such as the
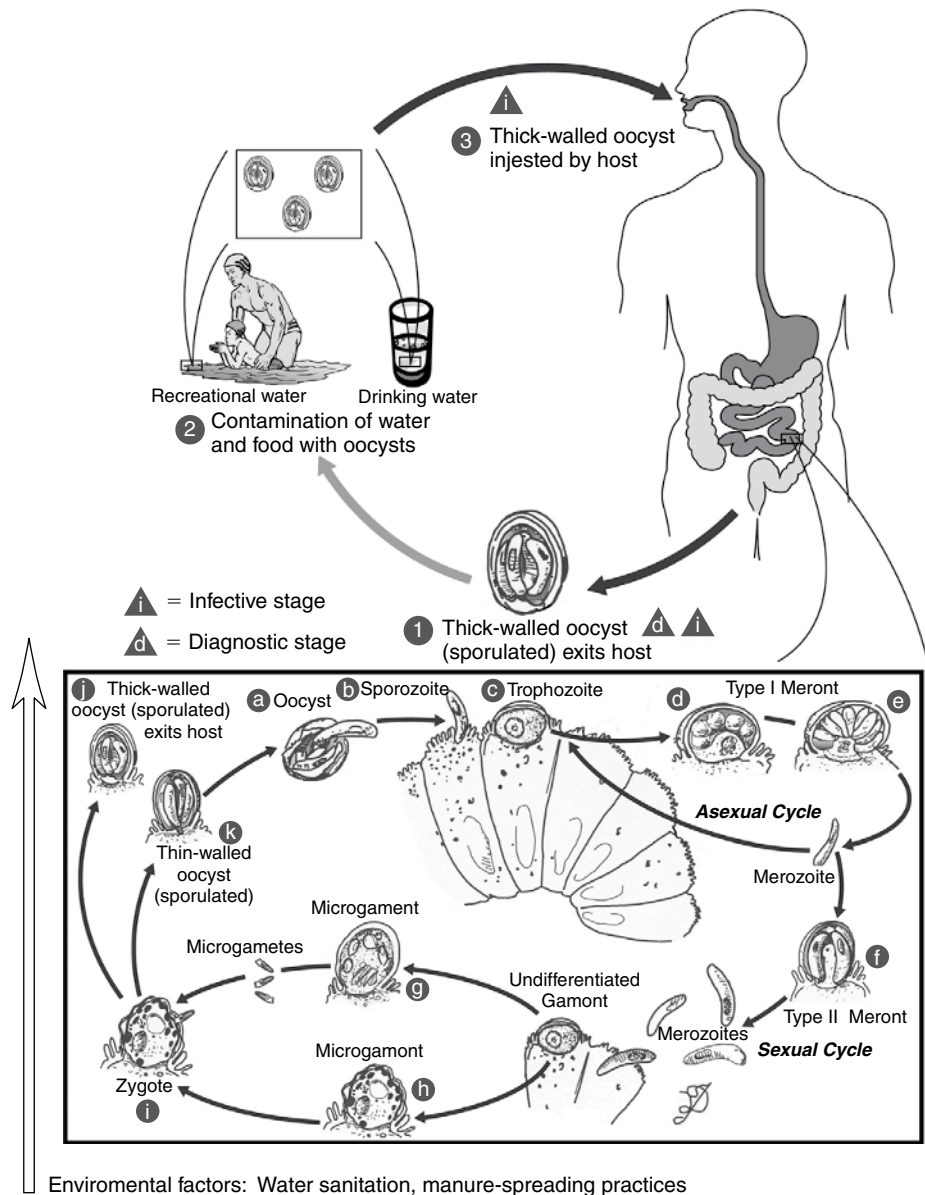
Figure 9-27 ■ Cryptosporidiosis transmission/life cycle. (Modified from Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)
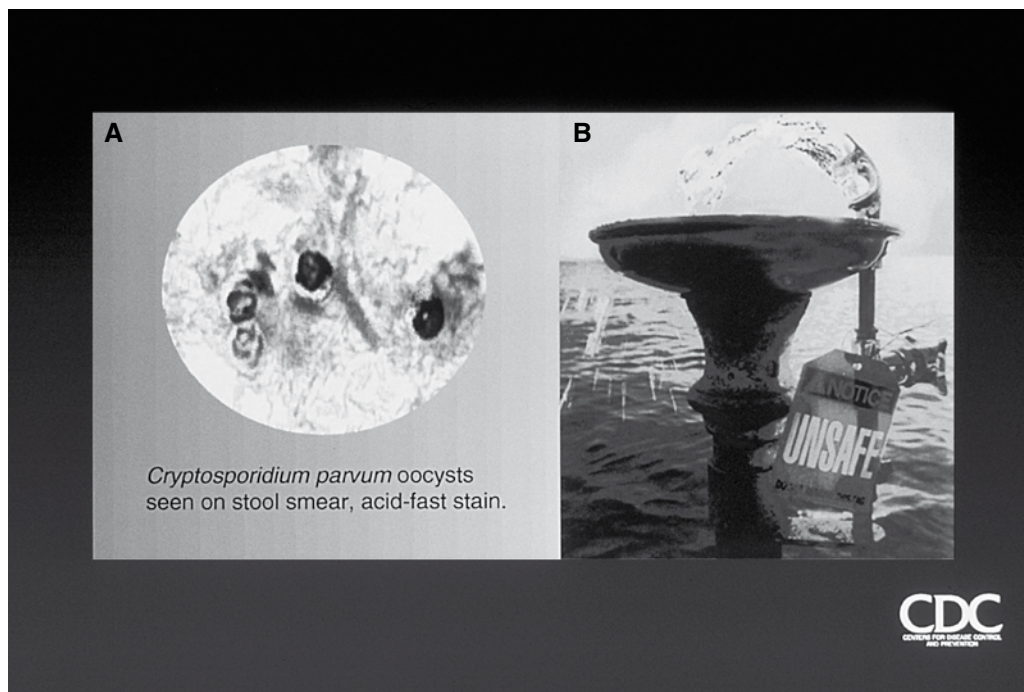
Figure 9-28 ■ **A,** Photomicrograph of *Cryptosporidium parvum* oocysts in stool smear, acid fast stain. **B,** Water fountain with sign that water is unsafe. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

sickening of more than 400,000 people in Milwaukee, Wis., due to improperly treated municipal water supply in 1993.[7] A secondary means of transmission is by inhalation of aerosolized oocysts.

Calves are accepted as a source for human infection. A study in Wisconsin using PCR analysis of human isolates concluded that most sporadic cases of cryptosporidiosis in that state were zoonotic in origin, with cattle and other ruminants the main source.[8] The types of zoonotic transmission that occur appear to differ by geographical area, with less zoonotic transmission occurring in urban areas. The risk of human infection by dogs and cats is believed to be small in industrialized countries. *C. canis*, *C. felis*, and *C. meleagridis* are responsible for as much as 20% of human infection in some developing countries, but some evidence indicates that although diseases originates in animals, these strains are being transmitted person to person.[4] Data from the Milwaukee outbreak and others suggest two thirds of water-source human outbreaks are not of animal origin. Transmission in animals, as in humans, occurs through ingestion and possibly inhalation of oocysts.

Environmental Risk Factors

Cryptosporidium cysts, like *Giardia*, can contaminate water supplies and other moist environments for months. Environments where manure is spread have been associated with increased risk of human infection.[9]

Disease in Humans

The majority of the North American population has been exposed to the infection at some time. *Cryptosporidium* infection in immunocompetent humans can be asymptomatic.

The major symptom is diarrhea—often explosive, profuse, and watery with mucus—accompanied by abdominal pain and cramping, vomiting, and weight loss.[3] Low-grade fever may occur. The diarrhea is self-limiting in healthy people, lasting 8 to 20 days. In patients infected with HIV and in other immunodeficient patients, symptoms can be more severe and chronic and include massive diarrhea and involvement of the respiratory and biliary tracts.[5]

Disease in Animals

In dogs and cats, the disease is often subclinical. Puppies and kittens are more likely than adults to show intestinal signs of infection. In cats and dogs, most clinical cases are associated with immunosuppression, such as with feline leukemia virus, canine distemper virus, canine parvovirus, and intestinal lymphosarcoma, and can manifest as intestinal, hepatic, pancreatic, or respiratory disease.[10] Calves may exhibit diarrhea, anorexia, and weight loss. Adults are often asymptomatic. Cryptosporidiosis commonly causes vomiting in snakes (Color Plate 9-11). Table 9-18 provides a comparison of clinical manifestations in humans and other animals.

Table 9-18 ▪ Cryptosporidiosis: Comparative Clinical Presentations in Humans and Other Animals			
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**
Humans	Children and their caretakers Farm animal contact	1-12 days[3]	Asymptomatic *or* acute watery diarrhea, coughing and low-grade fever
Dogs, cats, ruminants, mice, horses (*Cryptosporidium.* spp. can infect reptiles and birds)	Neonates, immunocompromised at increased risk of symptomatic disease	5-10 days	Often asymptomatic in older and immunocompetent animals Small-bowel diarrhea, diarrhea, tenesmus, dehydration, weight loss

Table 9-19 ▪ Antibiotic Treatment of Cryptosporidiosis in Humans and Other Animals		
Species	**Primary Treatment**	**Alternative Treatment**
Humans: immunocompetent	Supportive care Nitazoxanide 500 mg PO bid × 3 days[11]	
Adult with HIV infection	Effective antiretroviral therapy best treatment	
Dogs, cats	Supportive care Paromomycin 125-165 mg/kg PO bid × 5 days (may cause nephropathy in young animals)	Tylosin 11 mg/kg q12h × 28 days
Cattle	Supportive care, hyperimmune bovine colostrum	

Diagnosis

In human beings, cases are diagnosed by IFA visualization of oocysts in feces. An ELISA test is also available. Many laboratories do not routinely test for *Cryptosporidium*, so a special request may be necessary.

Animal diagnosis involves testing for oocysts in feces with sucrose or zinc sulfate solution with visualization after modified acid-fast staining, a procedure typically performed by a veterinary laboratory rather than by the private practitioner (Color Plate 9-12). Routine in-house flotation tests often fail because cysts are small (4 to 5 microns in diameter). To inactivate potential cysts and submit fecal samples to an appropriate laboratory, mix one part 100% formalin with nine parts feces. Oocysts are not shed continuously; therefore repeat samples may be necessary.

Treatment

Acute cryptosporidiosis is treated with supportive care including rehydration. Antibiotics are indicated for symptomatic patients. In patients with HIV infection, adequate antiretroviral therapy is essential to reducing the morbidity of cryptosporidiosis infection (Table 9-19).

In immunocompetent animals the disease is usually self-limiting and may include oral glucose-electrolyte solution. Severe diarrhea warrants parenteral fluids. If there are zoonotic concerns, a trial of antibiotics may be warranted. No antibiotics are registered for treatment of *Cryptosporidium* in animals. Monitor fecal oocyst shedding 14 days after treatment.

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DERMATOPHYTOSIS

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Dermatophytosis (ICD-10 B35)

Other names in humans: ringworm infection, tinea infection, dermatomycosis, trichophytosis, microphytosis

Other names in animals: ringworm, keratinophilic mycosis

Dermatophytosis is a skin infection caused by members of three genera of fungi: *Epidermophyton, Microsporum,* and *Trichophyton*. Because all domestic animals are susceptible to dermatophytosis and many dermatophytes can pass between species, dermatophytosis is probably one of the most common pet-associated and occupational zoonoses. It has been estimated that approximately 2 million people in the United States are infected each year as a result of contact with animals.[1] The true prevalence is probably greater than recognized; the signs of disease may be mild, so infected individuals may not seek medical care and the condition is often not reported to local health authorities.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide descriptive epidemiology about the disease.
- Educate the public on modes of transmission and risk factors for infection.
- Raise awareness of the disease among high-risk groups such as animal workers and in school settings.
- Make recommendations for environmental cleanup of contaminated surfaces and fomites with dilute bleach solution (1:10).

Human Health Clinicians

- When taking a history on a patient with a rash for which dermatophytosis is suspected, inquire about pet and other animal exposures.
- Teach patients to always wash their hands after contact with pets and other animals.[2]
- Encourage infected patients with dogs and cats to seek veterinary evaluation of their pets.
- No human vaccine is available.

Veterinary Clinicians

- Ensure that owners bring affected animals for prompt treatment; be aware that there are inapparent carriers and that use of corticosteroids may prolong infection.
- Counsel clients and veterinary care staff about handwashing and other measures to avoid zoonotic transmission.

- Counsel pet owners and clinic employees to disinfect contaminated equipment, bedding, and the environment with dilute bleach solution (1:10).
- Consider the possibility of rodents spreading the disease to pets and other animals.
- If dermatophytosis is diagnosed in a pet, treat the animal and advise the owner and family members of the zoonotic risk and to seek medical care if symptoms are noticed.
- Isolation may be advisable for an animal that is under treatment due to the zoonotic nature of the disease.
- An attenuated vaccine for cattle is available in Europe, where it has been reported to reduce the incidence of zoonotic disease in animal care workers[3]; it is not currently available in the United States.
- Therapy cats should be tested biannually.[4]

Agent

Fungi that cause dermatophytosis are spore-producing pathogens that may be classified according to mode of transmission as anthropophilic (preferring humans), zoophilic (preferring animals), or geophilic (preferring soil environments). Although zoophilic species often can pass from animals to humans, they tend to not be readily transmissible from human to human. Table 9-20 lists the main species and their type.[5]

Geographical Occurrence

These pathogenic fungi are found worldwide and the incidence is generally higher in hot and humid climates. *Trichophyton tonsurans* is commonly found in urban areas in the eastern United States, Puerto Rico, Mexico, the United Kingdom, and Australia. *T. verrucosum* and *T. mentagrophytes* are common in rural areas[2] as is *Microsporum canis. M. audonii* is more common in West Africa.

Groups at Risk

Dermatophytoses from animals are an occupational risk for veterinary health care workers and other animal workers. Pet owners, children, and immunocompromised individuals are at increased risk of infection,[2] as are humans living in close quarters (such as military personnel, athletes, school children, and inner-city residents) who are at risk for human-to-human transmission.

Hosts, Reservoir Species, Vectors

Table 9-20 lists the principal animal reservoir species for the *T. mentagrophytes* zoophilic dermatophytoses. The different species of fungi tend to vary in their host specificity. *M. nanum,* an infection of pigs, tends not to infect other species,[4] whereas *T. mentagrophytes* has a much wider host range, infecting rodents, dogs, cats, rabbits, horses, humans, hedgehogs,[6] and other animals. Mechanical vectors include furniture, animal bedding, hair care articles (scissors, combs, and brushes), clothing, and hats.

Table 9-20 ■ Classification of the Major Dermatophytes

Anthropophilic	Geophilic	Zoophilic	
		Organism	Sources
Trichophyton concentricum	*Trichophyton ajelloi*	*Trichophyton erinacei**	Hedgehogs
T. gourvilii	*T. terrestre*	*T. equinum*	Horses
*T. mentagrophytes interdigitale**	*Microsporum fulvum*	*T. mentagrophytes**	Rodents
T. megnini	*M. gypseum*	*T. quinckeanum**	Mice
T. rubrum		*T. simii*	Monkeys
T. schoenleinii		*T. verrucosum*	Cattle
T. soudanense		*Microsporum canis*	Cats, dogs
T. tonsurans		*M. gallinae*	Chickens
T. violaceum		*M. nanum*	Pigs
T. yaoundei		*M. persicolor*	Bank voles
Microsporum audouinii			
M. ferrugineum			
Epidermophyton floccosum			

*These organisms are part of the "mentagrophytes" complex and may be classified as a single species.
From Mandell GE, Bennett JE, Dolin R (eds): *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2000, Churchill Livingstone Elsevier.

Mode of Transmission and Life Cycle

Transmission occurs through direct skin-to-skin and skin-to-hair contact with infected animals or humans and indirect contact with the infectious arthrospores in the environment or on fomites (Figure 9-29). An infected human or animal can generate an aerosol of infectious arthrospores.[2] The infectious spores germinate in the keratinized layers of skin, hair, and nails.[7]

The mode of transmission also helps determine the severity of clinical disease. In general, animal-to-human transmission produces some of the most severe clinical syndromes, as shown in Table 9-21.

Environmental Risk Factors

The fungi and infectious spores can survive on surfaces and in desquamated skin for months.[2] Therefore environmental contamination can play an important role in transmission. In general, moist, warm environmental conditions favor the

Table 9-21 ■ Clinical Features of Dermatophytes Based on Mode of Transmission

Mode of Transmission	Clinical Features
Human-to-human	Mild to noninflammatory, chronic
Animal-to-human	Intense inflammation (pustules and vesicles possible), acute
Soil-to-human or animal	Moderate inflammation

From Bolognia JL, Jorizzo JL, Rapini RP (eds): *Dermatology*, ed 2, London, 2003, Mosby Elsevier.)

growth of fungi and persistence of spores on surfaces and articles. Environmental samples such as soil and clothing associated with human and other animal cases have spore positivity rates as high as 100%.[8] Contamination with multiple dermatophyte species has been found on veterinary clinic floors, producing an environmental risk of infection for both animals, clients, and the veterinary staff.[2]
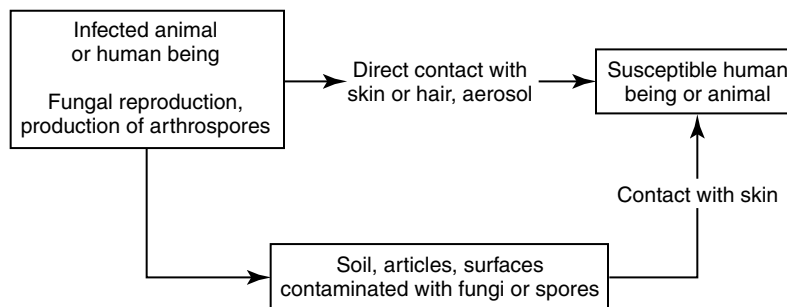
Environmental factors: Climate, temperature, humidity, crowding

Figure 9-29 ■ Transmission of dermatophytosis in animals and humans.

Disease in Humans

The incubation period in humans is 10 to 14 days. Infection in humans usually begins with a small area of erythema that develops into a patch of annular scaling skin with a raised border that then slowly spreads peripherally. Infections are usually accompanied by pruritus, which can lead to excoriation and secondary bacterial infections. As shown in Table 9-21, zoophilic fungi are more likely than anthropophilic or geophilic fungi to produce severe inflammatory changes in humans, often with pustular lesions (kerion).[9] The location of the infection determines the name of the dermatophytosis.

Tinea capitis is an infection of the scalp that occurs most commonly in children. It is caused by only two genera: *Trichophyton* and *Microsporum*. In the United States, *T. tonsurans* is the most common cause and *M. canis* is the second most common.[9] Tinea capitis can produce localized hair loss, pustules, and scarring (Figure 9-30).

Tinea corporis is an infection of the trunk and extremities that does not involve the hair, palms, soles, or groin. Worldwide, it is most commonly caused by *T. rubrum* followed by *T. mentagrophytes.*[9] It can present in a variety of ways dependent in part on the mode of transmission, but classically causes a circular annular lesion with scaling (Color Plate 9-13).

Tinea pedis is an infection of the toes and feet caused *T. rubrum*, *T mentagrophytes, Epidermophyton floccosum,* and *T. tonsurans.*[9]

Other dermatophyte infections include tinea barbae, an infection of the beard area; tinea cruris, an infection of the groin and perianal area; and tinea manum, an infection of the hand.

In immunocompromised individuals, *T. mentagrophytes* and *M. canis* can cause disseminated skin infection.

Disease in Animals

The incubation period in animals is generally 1 to 2 weeks. The infection in dogs may begin as alopecia (Figure 9-31). Erythema, scaling, and pruritus may develop around the lesions. In some dogs clinical signs do not develop yet the dogs are capable of shedding spores into the environment. In immunocompromised animals, these infections can be severe (Color Plate 9-14).

Up to 90% of infected cats show no clinical signs of disease. Clinical infections are more common in kittens and long-haired breeds of cats. Clinical signs include a poor hair coat or circular skin lesions, usually on the face or paws (Color Plate 9-15).

Infections are more common when cattle are stabled indoors. Lesions often begin as gray-white areas that thicken, scab, and slough, leaving an area of alopecia. Infection is often self-limited over several months (Color Plate 9-16).[3]

Horses tend to become infected at areas of contact with a harness. The disease manifests as areas of localized alopecia with skin thickening (Figure 9-32 and Color Plate 9-17).[3]

Figure 9-31 ■ Dermatophytosis. Focal alopecia on the muzzle of a Dachshund. This is a typical location for dogs that frequently dig in soil**.** (From Medleau L, Hnilica KA: *Small animal dermatology: a color atlas and therapeutic guide*, ed 2, St Louis, 2006, Saunders Elsevier.)

Figure 9-30 ■ Tinea capitis due to *M. canis* infection. (From Mandell GE, Bennett JE, Dolin R: *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2000, Churchill Livingstone Elsevier.)

Figure 9-32 ■ Classic signs of dermatophytosis (ringworm) in a horse. (From Reed SM, Warwick MB, Sellon DC: *Equine internal medicine*, ed 2, St Louis, 2004, Saunders Elsevier.)

Table 9-22 ■ Dermatophytosis: Comparative Clinical Presentations in Humans and Other Animals				
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**	**Laboratory Findings**
Humans	Children, crowding, contact with animals, immunocompromised	10 days to 2 wk	Erythema, itching, scaling lesion of skin	KOH preparation may show hyphae; Wood's lamp may fluoresce; fungal culture
Dogs or cats	Crowding, young animals, immunodeficiency	1-4 wk	Alopecia or poor hair coat, scales, erythema, asymptomatic	
Cattle	Stabling indoors, calves		Gray-white areas that scab and fall off, leaving alopecia	*M. canis* may fluoresce under Wood's lamp, microscopic examination[10] Fungal culture
Horses	Friction from harnesses		Dry, scaling, thickened areas	
Rodents			Often no clinical signs, white scabby lesions of head and trunk	

KOH, Potassium hydroxide.

Rodents such as mice may show no evidence of disease or may have white scabbing lesions on the head and trunk (Color Plate 9-18).

Table 9-22 shows the comparative clinical presentations in humans and animals.

Diagnosis

In humans the diagnosis can be made clinically based on the typical appearance of lesions and a history of contact with an infected person or animal. The differential diagnosis may include eczema, impetigo, and conditions causing localized alopecia, such as cutaneous lupus. The sensitivity and specificity of the Wood's lamp test is limited because only some dermatophytes will fluoresce; therefore this test should be used only as part of a screening process. Wood's lamp–positive areas can be used to guide scrapings for microscopic examination and/or culture. Samples of skin and hair should be taken from the periphery of lesions where infection is active.

Scrapings or clippings can be placed in 10% to 20% potassium hydroxide solution and examined microscopically. Hyphae can appear as chains (Figure 9-33). Conidae (spores) can also be recognized by microscopy (Figures 9-34 and 9-35).

In addition to microscopy, fungal culture is often worthwhile to confirm the diagnosis and the fungal species (Color Plate 9-19). Similar diagnostic tests are used in other animals.

Treatment

Table 9-23 outlines treatment guidelines in humans and other animals. Many human cases of dermatophytosis are self-limited and do not require treatment. However, treatment

Figure 9-33 ■ Photomicrograph of the fungus *Trichophyton mentagrophytes*. This dermatophyte is a zoophilic species that commonly inhabits mice, guinea pigs, kangaroos, cats, horses, sheep, and rabbits. Members of the genus *Trichophyton* are common causes of hair, skin, and nail infections in humans. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Dr. Leonor Haley.)

Figure 9-34 ■ *Trichophyton mentagrophytes* in culture. Spherical microconidia and one thin-walled, multicellular, cigar-shaped macroconidium (lactophenol analine blue, ×2000). (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy Spencer Jang, University of California, Davis.)
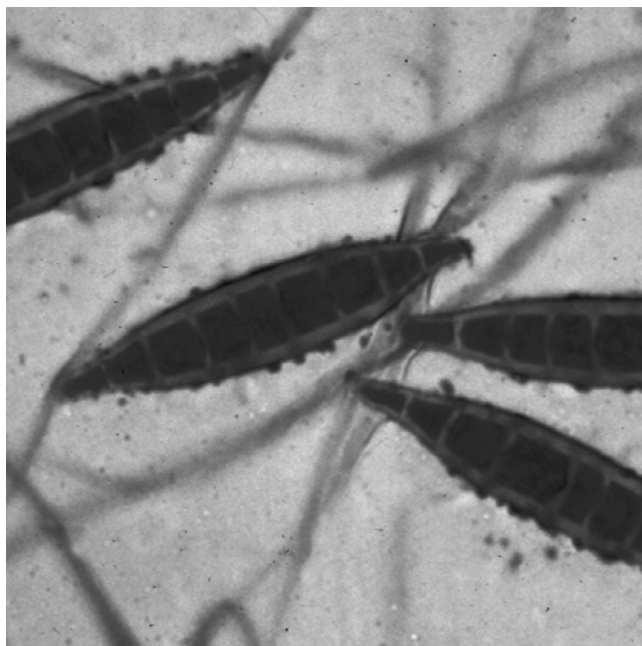
Figure 9-35 ■ *M. canis* in culture. Rough and thick-walled multicellular spindle-shaped macroconidia. Note curved, pointed ends (lactophenol analine blue, ×2000). (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy Richard Walker, University of California, Davis.)

may shorten the duration of infection and reduce the possibility of further transmission.

Companion animals with positive culture findings should be treated because of the zoonotic disease risk.[11] However, eradicating the disease may be a challenge if multiple animals are housed together. Response to therapy is monitored by dermatophyte culture as many animals will remain culture positive while improving clinically.

For mild skin infections, topical medication may be sufficient. More extensive infections may require systemic treatments. In food-producing animals, treatment options may be limited because of food safety concerns.

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Table 9-23 ■ Dermatophytosis Treatment in Humans and Other Animals

Species	Primary Treatment	Alternative
Humans: tinea corporis, tinea cruris, tinea pedis	Topical antifungal, drying powder	Terbinafine 250 mg PO × 4 wk *or* ketoconazole 200 mg PO q24h × 4 wk *or* fluconazole 150 mg PO 1×/wk for 2-4 wk *or* griseofulvin: *Adults:* 500 mg PO q24h × 4-6 wk *Children:* 10-20 mg/kg/day 2-4 wk for T. corporis, 4-8 wk for T. pedis
Humans: tinea capitis	*Adults:* Terbinafine 250 mg PO × 4 wk (*T. tonsurans*) or 4-8 wk (*M. canis*) *Children:* 125 mg or 6-12 mg/kg PO qd[12]	Itraconazole 3-5 mg/kg PO qd × 30 day *or* fluconazole 8 mg/kg (max 150 mg) PO qwk × 8-12 wk griseofulvin: *Adults:* 500 mg PO q24h × 4-6 wk *Children:* 10-20 mg/kg/day until hair regrows[12]
Dogs and cats (NOTE: Spontaneous remission may occur in short-haired cats in a single-cat environment and in dogs; environmental treatment is important; use dilute bleach [1:10]; multi-cat environments can be complicated.)	Topical miconazole or clotrimazole[10] Griseofulvin microsized formulation 25-60 mg/kg PO q12h × 4-6 wk (fed with a fatty meal helps increase absorption) Ultramicrosized formulation 2.5-5.0 mg/kg PO q12-24h Pediatric suspension 10-5 mg/kg PO q12h Lufenuron (Program) 100 mg/kg for 2 doses at 2-week intervals, then treat monthly Clipping and topical therapy: lime sulfur (1:16) or miconazole shampoo	Ketoconazole (not labeled for use in dogs and cats in the United States) 10 mg/kg PO q24h or divided twice per day for 3-4 wk; acid meal (add tomato juice) will enhance absorption Itraconazole 10 mg/kg PO q24h or 5 mg/kg q12h Spot treatment not recommended[11]
Cattle	Washes or sprays of 4% lime sulfur, 0.5% sodium hypochlorite bleach, 0.5% chlorhexidine, 1% povidone-iodine, natamycin, and enilconazole (not available in the United States)	Treat individual lesions with miconazole or clotrimazole lotions
Horses	Topical clotrimazole or miconazole	
Lambs	Sodium hypochlorite washes or enilconazole rinses[11]	

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DIPYLIDIASIS

Peter M. Rabinowitz and Lisa A. Conti

Dipylidiasis (ICD-10 B71.1)

Other names in humans: dog tapeworm

Other names in animals: dog tapeworm, dog cestodiasis

The dog tapeworm (*Dipylidium caninum*) is a common parasite of dogs and cats. The cat flea (*Ctenocephalides felis*) and dog flea (*Ctenocephalides canis*, relatively rare in North America)[1] are important intermediate hosts in the life cycle. Human infection is apparently a rare event that occurs when children ingest fleas containing tapeworm eggs.[2] Although infection in both humans and other animals is usually asymptomatic, the white, seedlike, motile proglottids are passed in the stool, causing concern.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Educate the public about the need for routine flea control.
- Ensure policies are in place for proper disposal of animal feces.

Human Health Clinicians

- The veterinarian caring for the family pets should be contacted to ensure that pets receive treatment.
- The appearance of proglottids in the stool of a child may be a sentinel event indicating probable flea infestation in the house as well as infection of a household pet. Human health clinicians should counsel adult patients or parents of pediatric patients to seek veterinary advice and preventive services to ensure that the house and pets of a patient are treated for fleas.
- Children should wash their hands after playing with pets. Children with pica behavior require careful supervision when playing in environments with pets.

Veterinary Clinicians

- Counsel pet owners to practice flea control.
- Deworm all dogs and cats in the household when infection is identified in one animal (typically because of passage of tapeworm segments in stool).
- Counsel owners of pets that have been diagnosed with tapeworms or fleas to watch for signs of infection in children in the household.

Agent

The double-pored dog tapeworm (*D. caninum*) is a Cestode that is the most common tapeworm of dogs and cats.[3] The adult worms may be as long as 70 cm and can live in the small intestine for up to 3 months. The adult worms consist of a head (scolex), neck, and chain of segments known as *proglottids* (Figure 9-36). New segments form at the neck and older segments are pushed back.[4] Each proglottid contains both male and female elements and can become full of eggs (gravid) and break off from the rest of the worm, to be shed in the feces. Fleas play an important role in the life cycle of the worm as intermediate hosts.

Geographical Occurrence

Worldwide.

Groups at Risk

Young children appear to represent most human cases because of their close contact with pets and greater likelihood
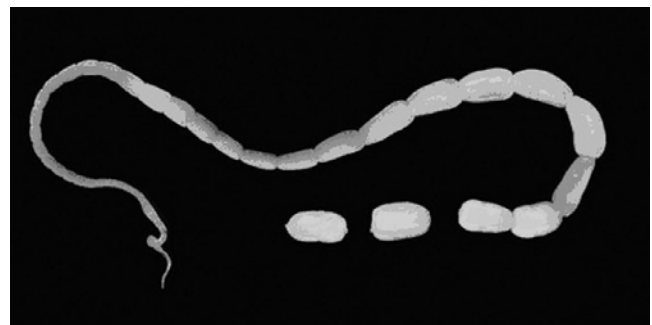
Figure 9-36 ■ Adult *Dipylidium caninum* with detaching proglottids. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

of ingesting fleas directly or in food. A case in a 5-week-old infant has been reported.[5]

Hosts, Reservoir Species, Vectors

Dogs and cats are the principal reservoirs, although wild carnivores have also been found to be infected. Humans are accidental hosts.

Mode of Transmission and Life Cycle

The adult worms live in the intestine of the reservoir host (Figure 9-37). Gravid proglottids are released in the feces (Figure 9-38). In the environment the proglottids break down, releasing the eggs. If the eggs are ingested by a larval cat or dog flea, the eggs hatch and turn into cysticercoids as the flea develops. Dogs and cats may ingest a flea as a defensive behavior. Children may ingest a flea accidentally when playing with or handling a dog or cat or by ingesting food containing a flea (Figure 9-39). Once the flea is ingested, cysticercoids are released into the small intestine, where they develop into adult worms within 20 days.[6]
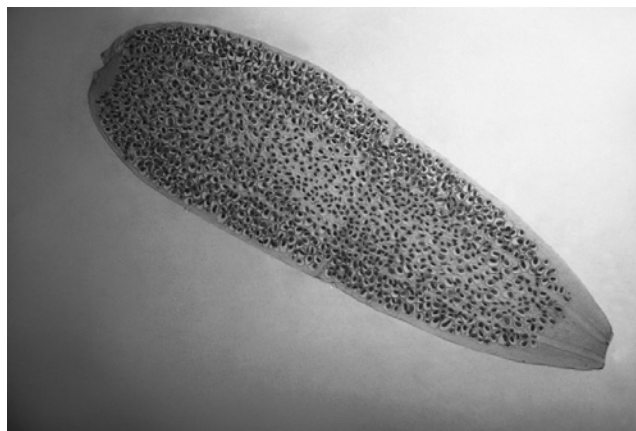
Figure 9-38 ▪ Micrograph depicting a proglottid (i.e., a tapeworm segment) from the Cestode *Dipylidium caninum*. Such proglottids, which when mature average 12 mm × 3 mm, are passed with feces and often resemble rice grains when dried. Each proglottid contains egg packets that are held together by an outer embryonic membrane. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)
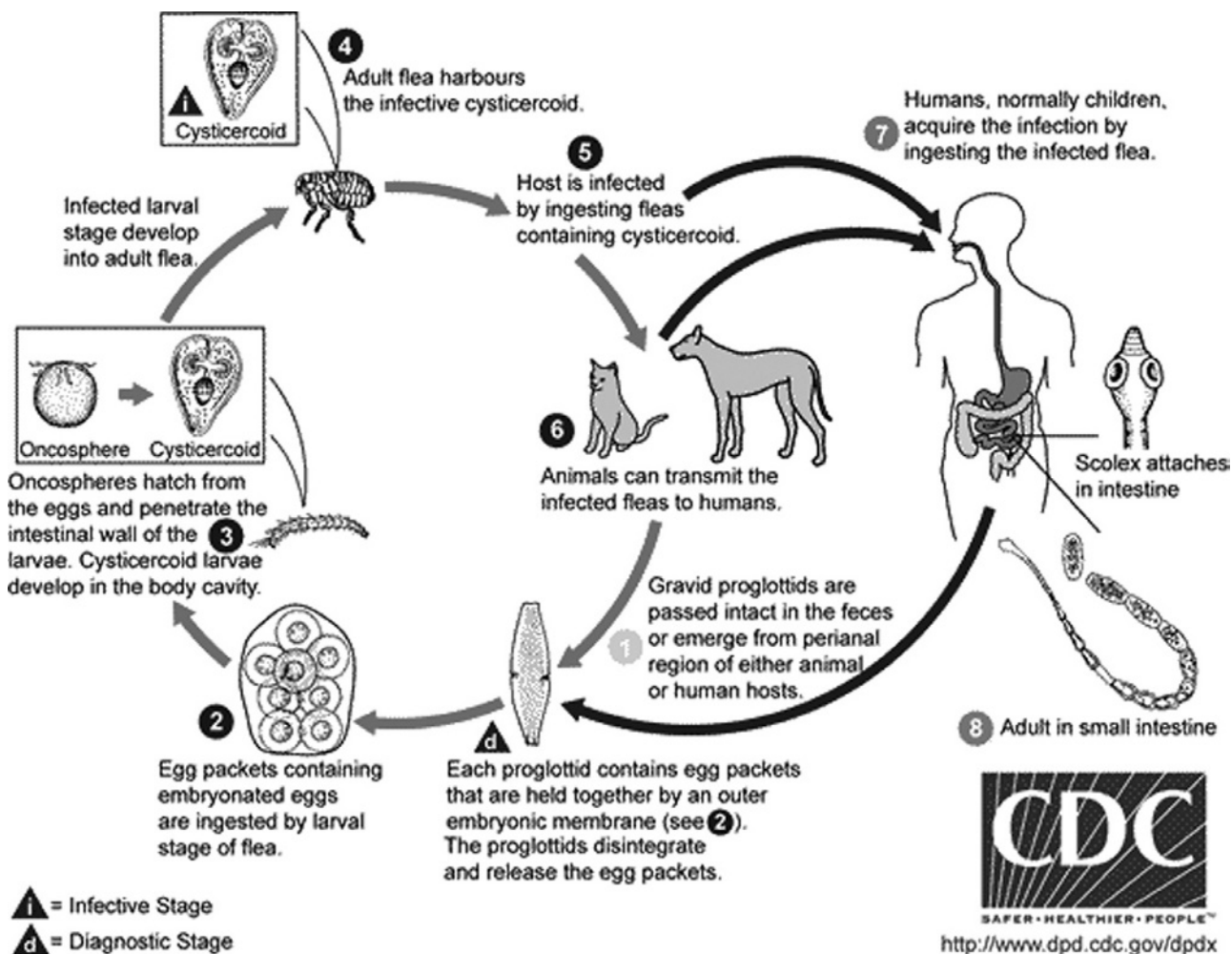
Figure 9-37 ▪ Life cycle, dipylidiasis. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)
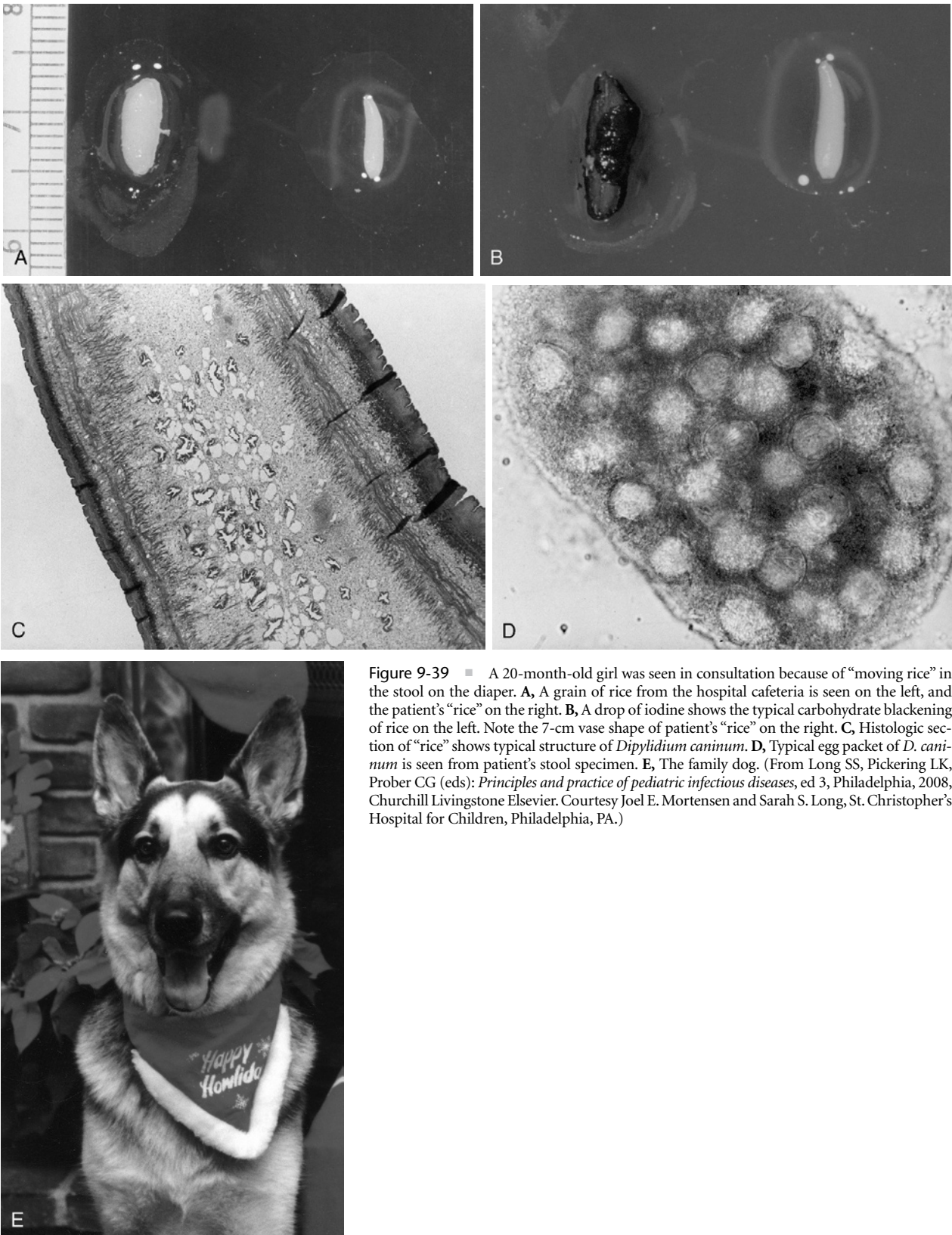
Figure 9-39 ▪ A 20-month-old girl was seen in consultation because of "moving rice" in the stool on the diaper. **A,** A grain of rice from the hospital cafeteria is seen on the left, and the patient's "rice" on the right. **B,** A drop of iodine shows the typical carbohydrate blackening of rice on the left. Note the 7-cm vase shape of patient's "rice" on the right. **C,** Histologic section of "rice" shows typical structure of *Dipylidium caninum*. **D,** Typical egg packet of *D. caninum* is seen from patient's stool specimen. **E,** The family dog. (From Long SS, Pickering LK, Prober CG (eds): *Principles and practice of pediatric infectious diseases*, ed 3, Philadelphia, 2008, Churchill Livingstone Elsevier. Courtesy Joel E. Mortensen and Sarah S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Table 9-24 ▪ Dipylidiasis in Humans and Animals				
Species	Risk Factors	Incubation Period	Clinical Signs	Diagnostic Findings
Humans	Fleas in house, children at increased risk of ingesting fleas	Adult worms develop in 20 days	Usually asymptomatic, may have abdominal pain	Proglottids in stool
Dogs, cats	Flea contact, ingestion		No symptoms or perianal pruritus	

Environmental Risk Factors

The key environmental risk is flea infestation of a house or other living environment.

Disease in Humans

Based on existing case reports, human infection with dipylidiasis is usually asymptomatic. The proglottids appear in the stool as white, rice-like motile objects and may be shed over a number of months. In one report, dipylidiasis was misdiagnosed as recurrent pinworm (*Enterobius vermicularis*) infection and therefore incorrectly treated.[7] Abdominal discomfort may occur, as well as abdominal distension, appetite disturbances, and insomnia.[6] Accompanying neurological symptoms including vertigo and light-headedness have been described.[8]

Disease in Animals

The infection in dogs and cats is considered to cause few clinical signs. Perianal pruritus may be present. Infected dogs may therefore "scoot," dragging their anus along the ground to relieve the itching. The most significant finding is the sight of proglottids in the feces, emerging from the anus or stuck to perianal hairs. These appear as white, crawling rice-like segments on the fur or in feces or on the perianal area.

Diagnosis

The diagnosis is usually made clinically by identifying the motile proglottids and obtaining a history of contact with fleas or a dog or cat. In animals, visualizing the proglottids of *D. caninum* is diagnostic. Table 9-24 shows the manifestation of disease in humans and other animals.

Treatment

The goal of treatment in humans and other animals is the elimination of the cestodes. Table 9-25 summarizes recommended treatment regimens for dipylidiasis in different species.

Flea control is also important for dogs and cats. This can be accomplished with monthly treatments of selamectin, lufenuron, imadacloprid, fipronil,[10] or spinosad.

Table 9-25 ▪ Treatment of Dog and Cat Tapeworm Infection in Humans and Other Animals		
Species	Primary Treatment	Alternative Treatment
Humans	Praziquantel 5-10 mg/kg PO × 1 dose	
Dogs*	Praziquantel 5 mg/kg PO, SC once	Praziquantel*/pyrantel/febantel PO once
	Flea control	Epsiprantel 5.5 mg/kg PO once
		Fenbendazole 50 mg/kg PO q24h × 5 days
Cats*	Praziquantel 5 mg/kg PO, SC once Flea control	Praziquantel/pyrantel PO once Epsiprantel 2.8 mg/kg PO once[10]

*Not for puppies or kittens younger than 3 weeks or weighing less than 2 lb.

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ECHINOCOCCOSIS

Peter M. Rabinowitz and Lisa A. Conti

Echinococcosis (ICD10B-67)

Echinococcosis due to **Echinococcus granulosus** *(ICD-10 B67-67.4), echinococcosis due to* **Echinococcus multilocularis** *(ICD-10 B67.9)*

Other names in humans: hydatid disease, cystic hydatid disease, alveolar hydatid disease, echinococciasis

Other names in animals: hydatid disease, hydatid cyst, unilocular hydatid disease, cystic echinococcosis, hydatidosis

Echinococcosis is a potentially fatal zoonotic tapeworm infection. Dogs and other canids are the definitive host of *Echinococcus granulosus*; therefore cases in humans are typically related to contact with domestic dogs. The types of human-dog contact and the way that dogs are raised and fed determine the degree of human risk.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide descriptive epidemiology regarding the risk in the community.
- Prevent dogs, cats, and foxes from contaminating playgrounds and other public areas with feces.
- Educate the public to thoroughly wash all fruits and vegetables before consuming them.
- Educate pet owners to not allow dogs and cats to roam outside or feed on raw carcasses.
- Ensure that workers with occupational risk for *Echinococcus* infection (e.g., sheep ranchers, wildlife rehabilitators) receive adequate surveillance and reduction of exposure risk through exposure controls and protective equipment.

Human Health Clinicians

- Disease is reportable in some states.
- Counsel dog owners to wash hands after handling pet and to avoid contact with animal feces.
- Counsel all patients to thoroughly wash vegetables and fruits before consumption.
- Ensure that high-risk groups (e.g., veterinarians, laboratory workers, and wildlife rehabilitators) frequently exposed to foxes and wild animals use protective measures (gloves and handwashing).

Veterinary Clinicians

- Counsel clients to avoid feeding raw meat to dogs and cats and to not allow pets to hunt.
- Train veterinary personnel in biosafety measures to reduce risk from infected dogs and wild animals.

- Regularly examine and treat high-risk dogs and cats (e.g., sheep dogs).
- An experimental recombinant vaccine is available for sheep in high-risk areas.

Agent

The causative agent of echinococcosis in humans is the larval (hydatid) phase of Cestodes (tapeworms) in the genus *Echinococcus*, including *E. granulosus*, *E. multilocularis*, *E. oligarthrus,* and *E. vogelii* (Figures 9-40 and 9-41).[1] Cystic echinococcosis is causes by *E. granulosus*, whereas *E. multilocularis* causes alveolar echinococcosis.

Geographical Occurrence

E. granulosus is found on every continent except Antarctica. In the United States, human cases are more likely to be found in areas where there is contact between dogs and sheep, such as in the western states. In Alaska, a sylvatic strain of *E. granulosus* is found in caribou and moose; dogs that eat the viscera of these infected animals can then infect humans.[2,3] *E. oligarthus* and *E. vogelii* are found only in Central and South America. Alveolar echinococcosis caused by *E. multilocularis* is restricted to the northern hemisphere.

Groups at Risk

Echinococcosis tends to occur in well-defined groups who have contact with dogs that ingest the raw viscera of infected animals. These include sheepherders who use dogs and persons in Alaska who allow dogs to feed on entrails of wild caribou and moose. Many of the cases diagnosed in the United States are in immigrants from countries where contacts between dogs and sheep and cattle are common.[4] Children may be at greater risk of infection because of close contact with dogs.

Figure 9-40 ▪ Scolex from hydatid cyst. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)
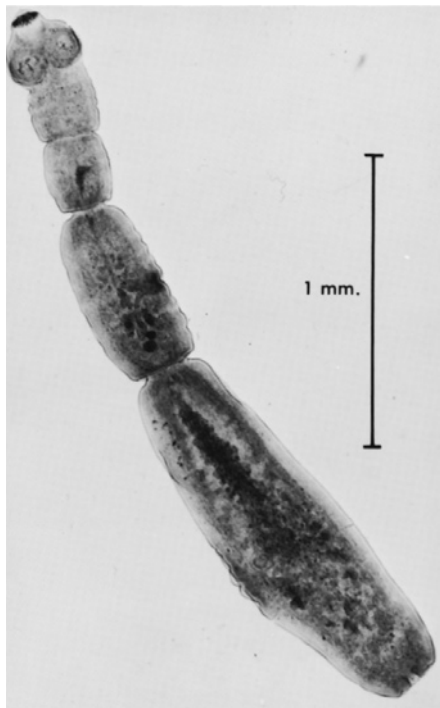
Figure 9-41 ■ *Echinococcus granulosus (*Taeniidae), entire worm (×44). (From Bowman DD: *Georgis' parasitology for veterinarians*, ed 8, St Louis, 2003, Saunders Elsevier.)

Reported risk factors for *E. multilocularis* infection include owning dogs that kill game or roam outdoors, living in a farmhouse or near a field, growing vegetables, owning outdoor cats, or eating unwashed fruit.[5]

Hosts, Reservoir Species, Vectors

Dogs and wild canids are the definitive hosts for *E. granulosus*. The adult tapeworms reproduce in the dog intestine and shed gravid proglottids or eggs in the feces. These eggs can remain viable in moist conditions with moderate temperatures for months. Intermediate hosts include a wide variety of herbivores as well as mongooses, non-human primates, and humans.

The growing urban populations of red and arctic foxes, the primary definitive host for *E. multilocularis,* increase concern for human risk of infection.[6] The intermediate hosts for *E. multilocularis* are usually rodents, including mice, shrews, lemmings, and voles.[7] In addition to foxes, dogs and cats that hunt such animals can subsequently infect humans.[8]

Mode of Transmission and Life Cycle

The adult tapeworms living in the intestine of a dog or other carnivore release eggs that are shed in the feces (Figure 9-42). Human infection occurs by ingesting these eggs, either through contamination of food or by direct contact with dogs or other definitive hosts. Children are often infected because of more intimate contact with dogs and frequent hand-to-mouth contact. Once ingested, the eggs hatch into larvae (oncospheres) in the small intestine. Migrating through the

intestinal wall, they lodge in the liver, lung, or other tissues. There they form cysts containing protoscolices. *E. granulosus* tends to form large, slowly growing unilocular cysts with a well-defined limiting membrane. By contrast, *E. multilocularis* form multilocular cysts, also known as "alveolar" cysts, without a limiting membrane and grow more aggressively.[4] This results in the potential for *E. multilocularis* to cause more serious complications. When dogs feed on the carcass of an intermediate host containing cysts, the protoscolices develop into adult worms in the dog intestine (Color Plate 9-20).

Environmental Risk Factors

Contamination of the environment by egg-containing feces of infected canids is an important factor in transmission of *Echinococcus*. Feces containing eggs can contaminate grazing areas of sheep and other ruminants, leading to infection of these animals.[8] *Echinococcus* eggs can survive in the environment for weeks to months under optimal conditions.[9]

Dogs that defecate near vegetable gardens or otherwise contaminate sources of food and water can be a source of infection for humans. Factors that increase the abundance of foxes and rodents (potentially infected with *E. multilocularis*) around dwellings can increase the risk of infection to humans and domestic animals; these can include the presence of food sources including pet food and bird seed from bird feeders.

Disease in Humans

Table 9-26 shows the clinical features of *Echinococcus* infection in humans and other animals.

Echinococcosis Caused by E. granulosus (Cystic or Unilocular Hydatid Disease)

The cysts tend to be slow growing, unilocular, and often asymptomatic for many years. The size may reach 15 cm or larger. Many cysts are discovered only during imaging performed for other reasons (Figure 9-43). The severity of disease depends largely on the organ involved and cyst size and number. Most hydatid cysts are found in the liver (50% to 70%) and lungs (20% to 30%) but more rarely can involve spleen, muscles, heart, kidney, and even the brain. Symptoms develop if a cyst becomes large enough to affect organ function or cause pain or if cysts rupture or become superinfected. Liver cysts can cause abdominal pain, whereas lung cysts can cause chest pain, cough, hemoptysis, and embolism.[7] Cyst rupture or leak suddenly, producing anaphylactic reactions, release of protoscolices, eosinophilia, and secondary infectious complications.[8]

Echinococcosis Caused by E. multilocularis

Cysts tend to grow more aggressively than those of *E. granulosus*, almost always involving the liver, but capable of forming metastases in other organs (Figure 9-44). Symptoms can include pain, jaundice, weight loss, and hepatic obstruction, with sometimes fatal complications. The clinical picture can thus resemble hepatic carcinoma. The World Health
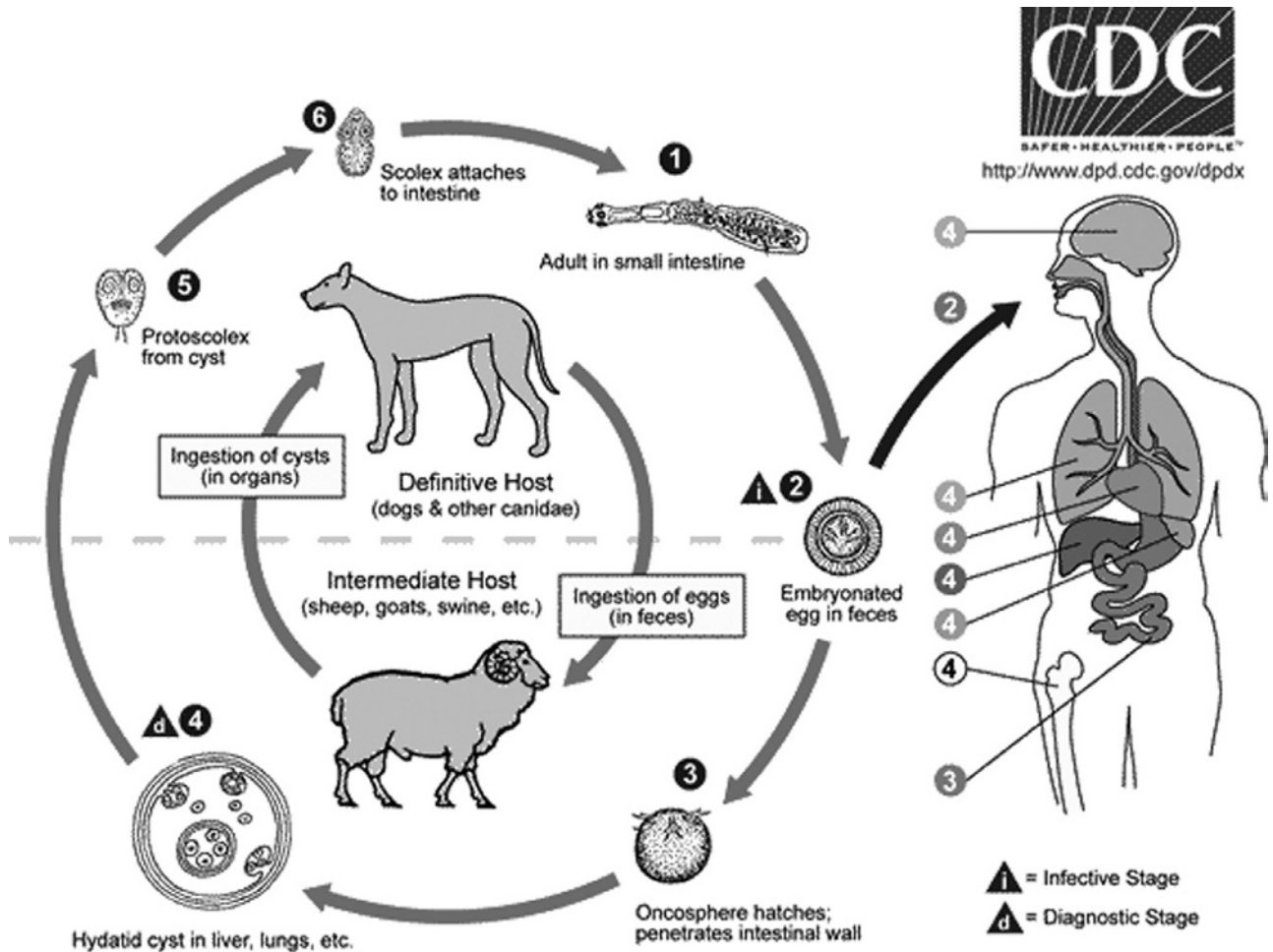
Figure 9-42 ▪ Life cycle/transmission, *Echinococcus granulosus* infection. *1,* Adult worms in bowels of definitive host. *2,* Eggs passed in feces, ingested by humans or intermediate host. *3,* Onchosphere penetrates intestinal wall, carried via blood vessels to lodge in organs. *4,* Hyatid cysts develop in liver, lungs, brain, and heart. *5,* Protoscolices (hydatid sand) ingested by definitive host. *6,* Attached to small intestine and growth to adult worm. (Modified from Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

Table 9-26 ▪ Clinical Presentation of Echinococcosis in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Diagnostic Findings
Humans: hydatid cyst disease	Children in rural areas, sheep herders with contact with dogs that feed on carcasses	12 months to years	Often asymptomatic, abdominal pain	Cyst seen on imaging, serology
Echinococcus multilocularis	Proximity to fox populations, ownership of dogs or cats that roam outside and feed on rodents		Pain, jaundice, weight loss, hepatic obstruction	Elevated bilirubin levels Irregular cysts on imaging, may have calcifications
Dogs	Feeding on infected carcasses or rodents	Adult worms produce eggs 27-61 days after infection[1]	Usually asymptomatic, enteritis with high parasite load	Fecal examination for eggs, adult worms, or proglottids
Sheep, goats, pigs, horses	Pastures contaminated with dog feces	Months to years	Usually asymptomatic, bloating may occur	Cysts on necropsy
Wild caribou, moose	Grazing areas contaminated by wolf, dog feces			
Rodents	Areas contaminated by feces of definitive host	Months	Symptomatic, fatal cysts may occur	
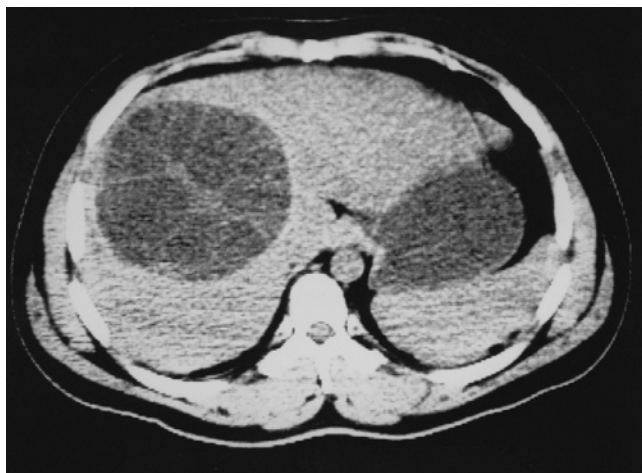
Figure 9-43 ■ CT image of large hydatid cyst in liver caused by *Echinococcus granulosus*. The membranes of multiple internal daughter cysts are visible within the primary cyst structure. (From Kliegman RM, Behrman RE, Jenson HB et al: *Nelson textbook of pediatrics*, ed 18, Philadelphia, 2007, Saunders Elsevier. Courtesy John R. Haaga, University Hospitals, Cleveland, Ohio.)

Figure 9-44 ■ CT image of alveolar cyst due *Echinococcus multilocularis* in right lobe of liver. Note irregular densities and areas of calcification. (From Long SS, Pickering LK, Prober CG: *Principles and practice of pediatric infectious disease*, ed 3, Edinburgh, 2008, Churchill Livingstone Elsevier.)

Organization (WHO) has devised a clinical staging system for alveolar echinococcosis based on parasitic mass, nodes, and metastases (PNM) similar to cancer tumor staging.[10]

Polycystic Hydatid Disease Cause by E. vogelii and E. oligarthus

These are comparatively rare infections that usually involve the liver or lungs and are characterized by the development of multiple microcysts.

Disease in Animals

Adult Cestode worms in the intestine of dogs, cats, and other definitive hosts rarely cause serious disease,[11] although large parasite burdens can result in signs of enteritis.

Figure 9-45 ■ A hydatid cyst *(Echinococcus granulosus)* in the liver of a horse (about natural size). This horse displayed no clinical signs of hepatic involvement despite the presence of 20 to 30 cysts like the one illustrated. (From Bowman DD: *Georgis' parasitology for veterinarians*, ed 8, St Louis, 2003, Saunders Elsevier.)

Intermediate hosts for *E. granulosus*, including sheep, goats, and horses, develop cystic disease that is generally subclinical, although jaundice, ascites, bronchopneumonia, decreased growth, and lameness have been reported (Figure 9-45 and Color Plate 9-21).[12] Rodents may develop clinical cystic disease from *E. multilocularis*.[1] Nonhuman primate deaths have been reported from zoologic institutions.

Diagnosis

The initial diagnosis is often made using ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). The differential diagnosis in human beings includes tumors, abscesses, and tuberculosis. When echinococcosis is suspected, serologic testing is performed using immunoblot or ELISA but is not 100% sensitive. Fine-needle aspiration of cyst contents can help make the diagnosis in equivocal cases by demonstrating protoscolices in the cyst fluid but carries a risk of cyst rupture and leakage.

In definitive host animals, arecoline purgatives can result in finding adult parasites or proglottids. In an experienced laboratory, fecal examination can reveal tapeworm eggs. A stool-based PCR test (copro-PCR) is also available.[13] In intermediate hosts, diagnosis can be made on histologic samples.

Treatment

Treatment of hydatid cyst disease in humans depends on the location of the cyst. While treatment is often surgical, the technique of puncture-aspiration-injection-reaspiration

Table 9-27 ▪ Echinococcus Infection: Treatment in Humans and Other Animals			
Disease Agent	**Species**	**Primary**	**Alternative**
E. granulosus	Humans	Puncture-aspiration-injection-reaspiration with albendazole before and after drainage (>60 kg; 400 mg PO bid; <60 kg; 15 mg/kg/day divided bid and for 28 days after[15])	Surgical drainage
E. multilocularis		Wide surgical excision, albendazole as for hydatid disease can be tried but efficacy unclear[15]	
	Dogs*	Praziquantel 5 mg/kg PO, SC once	Epsiprantel 5.5 mg/kg PO once
	Cats*	Praziquantel 5 mg/kg PO, SC once	Epsiprantel 2.8 mg/kg PO once[16]

*Not in animals younger than 4 weeks.

(PAIR) with the adjunctive use of an antihelminthic appears promising as an alternative for the treatment of uncomplicated cysts.[14] Albendazole is given before the procedure; then the cyst is aspirated and injected with hypertonic saline solution or alcohol and is then reaspirated with final irrigation. Albendazole treatment is then continued for 28 days. Such treatment produces cure in more than 90% of cases.[15] The treatment for alveolar echinococcosis is wide surgical excision, although albendazole can be tried in similar doses to that used in *E. granulosus* infection.

In the definitive animal host, tapeworms are treated with antihelminthics. Table 9-27 provides treatment information for humans and other animals.

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EHRLICHIOSES AND ANAPLASMOSIS

Peter M. Rabinowitz and Lisa A. Conti

Erlichioses and anaplasmosis (ICD-10 A79.8)

Other names in humans: human monocytic ehrlichiosis (HME), human granulocytic anaplasmosis (HGA), ehrlichiosis ewingii

Other names in animals: canine monocytic ehrlichiosis, canine hemorrhagic fever, tropical canine pancytopenia, canine rickettsiosis, tracker dog disease, canine typhus, tick-borne fever, pasture fever, equine anaplasmosis, Potomac horse fever, equine monocytic ehrlichiosis, infectious canine cyclic thrombocytopenia

Ehrlichiosis and anaplasmosis refer to several potentially serious tickborne diseases caused by related members of the family Anaplasmataceae. These diseases are transmitted to people and domestic animals by specific ticks that become infected by feeding on wildlife reservoirs. Recent taxonomic changes have reclassified some of these agents formally broadly called *Ehrlichia* into two genera; *Ehrlichia* and *Anaplasma.* New accepted terminology to describe these diseases in humans includes *ehrlichiosis* to refer to diseases caused by infection with *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, and *anaplasmosis* to describe disease caused by *Anaplasma phagocytophilum.* There are a number of similar diseases in dogs and other animals. Anaplasmataceae provide an excellent example of the need for animal and

human health professionals to work together since they were recognized as animal pathogens several decades before being described in human infection.[1] As with several other zoonotic diseases, recent advances in molecular diagnostics are shedding new light on the true prevalence of infection and the degree of overlap between human and animal ehrlichioses. Discoveries using animal models of infection with these agents also may further our understanding of diagnostic and treatment options in humans.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide epidemiologic analysis of these reportable diseases and assessment of local ehrlichiosis and anaplasmosis disease risk for the health district.
- Educate the public to:
    - Avoid tick-infested areas, but if this is not possible, wear appropriate clothing (long sleeves, long pants, tuck pants legs into socks, and wear light-colored clothing to visualize ticks). Wash clothes with hot water.[2]
    - Use CDC-recommended tick repellents such as DEET or permethrin (apply to clothes, not skin) where ticks are abundant. Be sure to follow label instructions before using any repellent.
    - Do frequent tick checks to remove even tiny immature-stage ticks.
    - Encourage adults to inspect children at least once daily for ticks. When in heavily infested areas, inspect children every 3 to 4 hours.
    - Use appropriate technique to remove ticks. Wear gloves or grasp tick with tweezers as close to the skin as possible and pull gently, or use a tick-removal spoon. Follow-up by cleaning the area, applying antibiotic topical on tick bite site, and washing hands.[3]
    - Discourage the use of matches, petroleum products, or nail polish as tick removal methods.[3]
    - Implement integrated pest management techniques including landscape management (Box 9-3). Counsel pet owners to discuss tickborne disease prevention strategies with their veterinarian.
- Work with local planning agencies on smart growth to avoid fractionating forested areas (see Chapter 6, Built Environment).

Human Health Clinicians

- Report cases of disease to public health authorities using the appropriate case definition: http://www.cdc.gov/ncphi/disss/nndss/casedef/ehrlichiosis_2008.htm.
- Counsel patients to avoid tick exposure or advise about use of appropriate tick repellents.
- Inquire about occupational risk factors for infection and ensure that workers at risk are educated about

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BOX 9-3 — *INTEGRATED PEST MANAGEMENT TO REDUCE TICK POPULATIONS AROUND DWELLINGS*

Some actions to consider in an integrated pest management approach include:
- Keep grass mowed.
- Remove leaf litter, brush, and weeds at the edge of the lawn.
- Restrict the use of groundcover, such as pachysandra, in areas frequented by family and pets.
- Remove brush and leaves around stone walls and wood piles.
- Discourage rodent activity. Clean up and seal stone walls and small openings around the home.
- Move firewood piles and bird feeders away from the house.
- Use veterinary-approved tick prevention products on pets; perform daily tick checks on pets and safely remove and dispose of ticks.
- Use plantings that do not attract deer, or exclude deer through various types of fencing.
- Move children's swing sets and sand boxes away from the woodland edge and place them on a wood chip or mulch-type foundation.
- Trim tree branches and shrubs around the lawn edge to let in more sunlight.
- Adopt hardscape and xeriscape (dryer or less water-demanding) landscaping techniques with gravel pathways and mulches. Create a 3-foot or wider wood chip, mulch, or gravel border between lawn and woods or stone walls.
- Consider areas with decking, tile, gravel, and border or container plantings in areas by the house or frequently traveled.
- Widen woodland trails.
- Consider a least-toxic pesticide application to tick-infested areas of high human exposure.

Adapted from Stafford KC: *Tick management handbook: an integrated guide for homeowners, pest control operators, and public health officials for the prevention of tick-associated disease,* revised edition, 2007, The Connecticut Agricultural Experiment Station, The Connecticut General Assembly, Bulletin No. 1010.

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tickborne disease prevention measures and are taking precautions.
- Ask patients about occurrence of tickborne disease in their pets.
- No ehrlichial vaccine is currently commercially available for humans.

Veterinary Clinicians

- Counsel clients to use protection (e.g., gloves, tick removal devices) when removing ticks from pets.
- Counsel owners about the potential for human infection related to shared environmental exposures, especially upon identification of seropositive pets.
- Treat pets preventively against ectoparasites.
- An equine vaccine against *Neorickettsia risticii* (formerly *Ehrlichia risticii)* is commercially available in the United States.

Agent

A number of related agents cause ehrlichioses and anaplasmosis in humans and other animals. These agents are gram-negative, obligate intracellular coccobacilli bacteria that
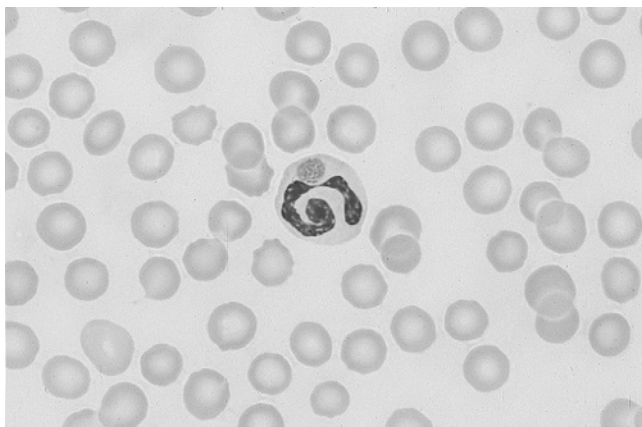
Figure 9-46 ■ A canine neutrophil containing an *Ehrlichia ewingii* morula. (Wright's stain, original magnification ×250.) (From Cowell RL, Tyler RD, Meinkoth JH et al (eds): *Diagnostic cytology and hematology of the dog and cat*, ed 3, St Louis, 2008, Mosby Elsevier.)
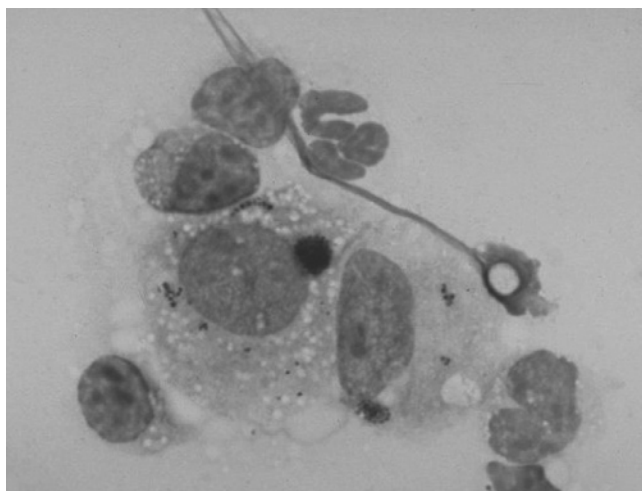

Figure 9-47 ■ *Ehrlichia* inclusion in the mononuclear cell of a cat. (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy Mike Lappin, Colorado State University, Fort Collins, Colo.)

parasitize leukocytes, erythrocytes, endothelial cells, or platelets (Figures 9-46 and 9-47). The bacteria within the family *Anaplasmataceae* that have been documented to cause disease in humans are *Ehrlichia chaffeensis, Anaplasma phagocytophilum, Ehrlichia ewingii, Ehrlichia canis,* and *Neorickettsia sennetsu.*

E. chaffeensis affects monocytic phagocytes, and the disease it causes in humans was formerly termed *human monocytic ehrlichiosis* (HME) but is now most commonly referred to as ehrlichiosis. *E. chaffeensis* is mainly a human pathogen but also causes diseases in dogs. *E. ewingii* is found in neutrophils, especially in immunocompromised patients.[4] It was formerly in the disease category "human ehrlichiosis, unspecified" and now is described as *E. ewingii* ehrlichiosis when it causes disease in humans; it has also been found to cause canine infections. The organism *A. phagocytophilum* (which

now includes the agent formerly called *E. equi*) also infects neutrophils. The disease in humans was formerly termed *human granulocytic ehrlichiosis* (HGE); it is now referred to as *human granulocytic anaplasmosis* (HGA) or, most commonly, simply *anaplasmosis.* Strains of *A. phagocytophilum* also cause disease in dogs, horses, ruminants and, rarely, cats.[5] *A. platys* is a canine pathogen that infects platelets and causes a disease known as *infectious canine cyclic thrombocytopenia*; it is not thought to be a significant human pathogen. Another canine pathogen, *E. canis*, causes ehrlichiosis in dogs; although it is not considered a highly likely zoonotic agent, at least one case of human infection with *E. canis* has been reported.[6] *Neorickettsia sennetsu* causes a febrile syndrome (sennetsu fever) that is rare outside Asia.[7]

Geographical Occurrence

The distribution of both human and domestic animal cases of the various ehrlichioses and anaplasmosis varies largely depending on the distribution of tick vector and reservoir species (Color Plate 9-22). For instance, although human cases of *E. chaffeensis* have been reported in almost every state in the United States, cases are most frequently reported from the southeastern and Midwestern states where white-tailed deer *(Odocoileus virginianus)* and Lone Star ticks *(Amblyomma americanum)* coexist. *E. chaffeensis* is restricted to the United States. *A. phagocytophilum* is found internationally in association with the distribution of *Ixodes* ticks. In the United States, human cases of *A. phagocytophilum* occur particularly in the upper Midwest, Northeast, and West Coast, where the primary vectors *Ixodes scapularis* and *Ixodes pacificus* exist; the distribution of infection is similar to that of Lyme disease. Although dogs seropositive for *E. canis* have been found throughout most of the United States, most canine cases occur in areas with an increased concentration of the brown dog tick *(Rhipicephalus sanguineus)* such as the southeastern states and the Southwest. In the United States, *E. canis* is mainly found in the Gulf Coast states and Eastern Seaboard, Midwest, and California.[8]

Groups at Risk

As in other tickborne diseases, the risk of ehrlichioses and anaplasmosis varies between and within regions and is generally related to the abundance of host ticks that can carry the disease. Individuals living in areas of high tick abundance are at increased risk. Immunocompromised individuals are at risk of infection with severe disease.

Hosts, Reservoir Species, Vectors

Infected animals are not believed to pose a substantial direct zoonotic risk to humans. In general, animal infections serve as a means of sustaining infections in tick vectors, and humans and other animals acquire infection from tick bites. White-tailed deer *(O. virginianus)* are considered a likely major reservoir for *E. chaffeensis* and *E. ewingii,*[4] and dogs may also play a role. The primary reservoir for *A. phagocytophilum* consists of small mammals, including deer mice *(Peromyscus)* and wood rats *(Neotoma)*, although deer may

also play a role.[9] Vectors of *A. phagocytophilum* are ticks of the genus *Ixodes,* including *I. scapularis, I. ricinus, I. pacificus, I. triangulaceps, I. spinipalpis,* and *I. persulcatus* (Color Plate 9-23).[4] These hard ticks are also the vector for *Borrelia burgdorferi, Babesia microti,* and tickborne encephalitis; therefore coinfection is common. The vector for *E. chaffeensis* and *E. ewingii* is the Lone Star tick (*A. americanum*). In dogs, the brown dog tick (*R. sanguineus)* is the principal vector for *A. platys* and *E. canis.*[10] *Dermacentor variabilis,* the American dog tick, can also be a vector of *E. canis* infection.[11] Accidental hosts for these agents include humans, dogs, cats, and ruminant animals.

Mode of Transmission and Life Cycle

Most ehrlichioses are tickborne infections. The larval, nymphal, and adult forms of the tick vectors are capable of transmitting infections. Figure 9-48 shows the life cycle of infection for *E. chaffeensis.* Most infections in the United States occur between May and August, coincident with periods of peak tick feeding activity.[9] Direct transmission between humans and other mammals has not been reported.

Environmental Risk Factors

The relation of environmental factors to the risk of anaplasmosis and ehrlichiosis may resemble that for Lyme disease, with landscape modification in the United States related to suburbanization of the human population playing a significant role. These suburban developments encroach into land that was previously forest habitat and result in "fragmentation" of forests (see Chapter 6). This provides habitat for deer and small mammals that can serve as reservoirs for certain *Ehrlichia* and *Anaplasma* and also increases tick abundance and infection rates.

Rights were not granted to include this figure in electronic media. Please refer to the printed publication.

Figure 9-48 ■ Life cycle/transmission, *E. chaffeensis.* Noninfected larvae obtaining blood from a bacteremic vertebrate reservoir host (e.g., white-tailed deer [*shaded*]), become infected, and maintain Ehrlichieae to the nymphal stage. Infected nymphs may transmit *E. chaffeensis* to susceptible reservoir hosts (unshaded) or to humans during acquisition of blood. Infected adult ticks, having acquired Ehrlichieae either by transtadial transmission from infected nymphal stage or during blood meal acquisition as noninfected nymphs on infected deer, may also pass *E. chaffeensis* to humans or other susceptible reservoirs. Transovarial transmission has not been demonstrated, and eggs and unfed larvae are presumably not infected. (From Paddock CD, Childs JE: *Ehrlichia chaffeensis*: a prototypical emerging pathogen, *Clin Microbiol Rev* 16(1):37, 2003.)

Climate change with warmer winters may also be leading to increased tick abundance during the following spring and summer.[12] Wild birds may play a role in dispersing the *Ixodes* tick vectors that can transmit *A. phagocytophilum*.[13]

Disease in Humans

Human ehrlichioses caused by *E. chaffeensis, E. ewingii*, or *E. canis* and anaplasmosis (HGA) caused by *A. phagocytophilum* can present as clinical syndromes that share a number of common features, including fever, headache, and myalgias, with laboratory findings of thrombocytopenia, leukopenia, and elevated liver function test results.

Rash is not a common feature of all ehrlichioses and anaplasmosis, although it may occur in up to 30% of children with *E. chaffeensis* infections. When present, it is maculopapular, not petechial.[14] *E. chaffeensis* may cause more severe disease than the other pathogens, and CNS involvement may occur in up to 20% of cases, including meningitis and meningoencephalitis. Septic shock and respiratory distress syndrome can also develop in patients with *E. chaffeensis.* Severe complications and even death are more common among immunocompromised patients. The overall mortality rate of *E. chaffeensis* disease is approximately 3%.[9] Coinfections with other agents sharing the same tick vector are not uncommon; therefore Lyme disease, babesiosis, or tickborne encephalitis may be seen in up to 10% of *E. chaffeensis* cases.[9]

Peripheral neuropathy may develop in patients with *A. phagocytophilum*, but severe complications and fatalities are less common (case fatality rate approximately 0.7%) than with *E. chaffeensis*.

Disease in Animals

Canine ehrlichiosis is a multisystemic disorder that can cause a variety of clinical signs, including fever, anorexia, CNS signs, hemorrhagic conjunctivitis, vasculitis, splenomegaly, and lymphadenopathy (Color Plates 9-24 to 9-27). The course of the infection may be subclinical, acute, or chronic.[15] Although cases of canine ehrlichiosis confirmed via cytology or serology have been attributed to *E. canis*, it is now thought that some cases may have been related to infections with *E. chaffeensis*, *E. ewingii,* or *A. phagocytophilum*.[16] Doberman pinschers and German shepherd dogs are considered by some to be more likely than other breeds to have severe chronic *E. canis* infection.[15] *E. ewingii* causes polyarthritis with fever and hepatosplenomegaly in dogs.[15] Concurrent infection with other *Ehrlichia, Anaplasma, Babesia, Haemobartonella,* or *Hepatozoon* organisms can worsen the clinical course of ehrlichiosis in dogs.

Canine anaplasmosis caused by *A. phagocytophilum* is thought to produce a milder clinical syndrome with fever, lethargy, and thrombocytopenia. *A. platys* causes a moderate to severe cyclic thrombocytopenia in dogs; however, bleeding complications are rare.[15]

Clinical ehrlichiosis has also been described in cats. Although the species of *Ehrlichia* that naturally infects cats has not been fully determined, clinical illness with signs including fever, anorexia, pale mucous membranes, and weight loss has been described.[16] A few cases of feline *A. phagocytophilum* infections, also known as *feline granulocytotropic anaplasmosis*, have been described in cats. Clinical signs associated with these infections include fever, anorexia, and lethargy.

A. phagocytophilum causes tickborne fever (also known as *pasture fever*) in cattle, sheep, and other ruminants, predominantly in Europe (Figure 9-49). The clinical signs are listed in Table 9-28. Equine anaplasmosis (formerly *equine ehrlichiosis*) is also caused by *A. phagocytophilum* (formerly *E. equi*) and consists of a febrile disease resembling human anaplasmosis. Table 9-28 shows the comparative clinical presentations in humans and other animals.

Diagnosis

Diagnosis in Humans

Ehrlichial infections in humans can resemble other tickborne febrile syndromes. A history of a tick bite and thrombocytopenia, leukopenia, and elevated liver function test results favor the diagnosis. Unlike Rocky Mountain spotted fever (RMSF), vasculitis is not present in ehrlichial infections.[14] In HME, rapid laboratory diagnosis is possible when cellular stippling of intracytoplasmic inclusions (morulae) in monocytes are seen, although this is uncommon (see Figure 9-49), while in HGA, morulae in neutrophils and bands can be seen more commonly (in up to 20% to 80% of cases[14]; Color Plate 9-28 and Figure 9-50). A PCR test using ethylenediamine tetraacetic acid (EDTA) or citrate-anticoagulated blood is becoming the standard method of diagnostic confirmation for both conditions.[14] The organisms can also be grown in cell cultures but this may take several weeks. Serologic tests using a fluorescent antibody reaction can be used to compare acute and convalescent titers, and demonstration of a fourfold change in titers is considered the most sensitive method of detecting infection, although the test may cross-react with

Figure 9-49 ■ Chronic weight loss in a goat as a sequela to anaplasmosis. (From Pugh DG: *Sheep & goat medicine*, St Louis, 2002, Saunders. Courtesy Tom Powe and D.G. Pugh, Auburn University, Auburn, Ala.)

Table 9-28 ■ Ehrlichioses and Anaplasmosis: Comparative Clinical Presentations in Humans and Other Animals

Species	Agent	Risk Factors	Incubation Period	Clinical Manifestations	Lab Findings
Humans					
Human ehrlichiosis (HME)	Ehrlichia chaffeensis, E. ewingii E. canis[17]	Tick exposures	7-10 days	Fever, myalgias, rash, respiratory distress, CNS and hepatic involvement	Thrombocytopenia, leukopenia, elevated liver function tests, morulae in monocytes (rare)
Human anaplasmosis (HGA)	Anaplasma phagocytophilum		7-14 days[4]	Fever, myalgias, peripheral neuropathies	Thrombocytopenia, leukopenia, morulae seen in neutrophils, bands (20%-80% of cases)[14]; elevated liver function tests[4]
Dogs					
Canine ehrlichiosis	E. canis, E. chaffeensis, E. ewingii	Tick exposures, animals allowed to roam outdoors	1-3 weeks[15]	May be subclinical, acute, or chronic; vasculitis, ataxia, hemorrhagic conjunctivitis, hepatosplenomegaly, lymphadenopathy, polyarthritis	Leukopenia, anemia
Canine anaplasmosis	A. phagocytophilum			Mild illness: fever, lethargy	Thrombocytopenia[15]
Infectious cyclic canine thrombocytopenia	A. platys			Moderate to severe thrombocytopenia, bleeding rare	Thrombocytopenia
Cats	A. phagocytophilum, E. canis	Tick exposures, animals allowed to roam outdoors		Rare; fever, anorexia, lethargy	Thrombocytopenia, leukopenia, anemia
Cattle, Sheep, Goats, Deer					
Tickborne fever (Pasture fever)	A. phagocytophilum	Tick exposures in endemic areas	2-6 days	Fever, lethargy, weight loss, decreased lactation, abortion, lymphadenopathy	Neutropenia, lymphocytopenia, thrombocytopenia[10]
Horses					
Equine anaplasmosis	A. phagocytophilum		10-45 days	Fever, ataxia, depression	Morulae seen in neutrophils

other diseases, including Lyme disease and RMSF.[9] PCR testing may help resolve problems of cross-reactivity between species that can occur with serology testing.

Diagnosis in Animals

In dogs, serology using IFA is commonly used with titers is more reliable 3 weeks after infection. Although IFA is sensitive, the test may not be very specific because of cross-reactivity between *E. ewingii* and *E. canis,* as well as *E. canis* and *A. phagocytophilum.* Standardized serologic tests for feline patients are needed. Depending on the ehrlichial species, cytology may be a useful tool for detecting the presence of morulae in blood or tissue smears. Depending on the type of animal and ehrlichial species, any one or a combination of other testing such as PCR, serology, immunoblotting,

and organism cultivation may be useful in confirming the diagnosis.

Treatment

Antibiotic treatment of ehrlichial infection in humans and other animals is shown in Table 9-29.

Treatment in Humans

Because of the serious nature of *Ehrlichia* and *Anaplasma* infections, early initiation of antibiotic treatment is recommended when the diagnosis is suspected. Doxycycline is considered the first line of treatment (see Table 9-29). In pregnancy, rifampin has been recommended by some authorities.
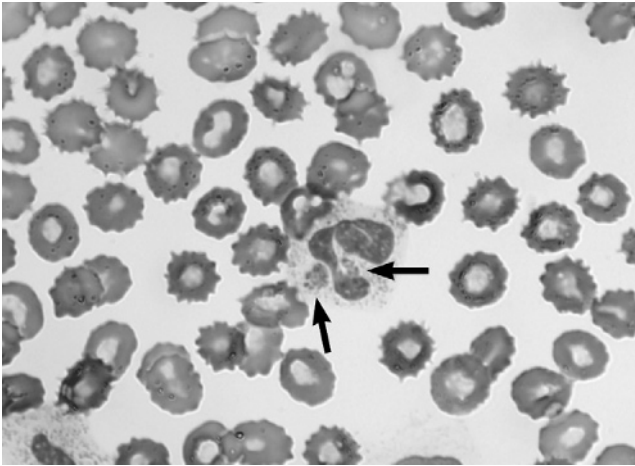
Figure 9-50 ■ Peripheral blood smear showing intracellular inclusion within a neutrophil of a patient with human granulocytic anaplasmosis (*arrows*). (Wright stain, ×1000.) (From Mandell GL, Bennett JE, Dolin R (eds): *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2005, Churchill Livingstone Elsevier.)

Table 9-29 ■ Antibiotic Treatment of Ehrlichial Infection in Humans and Other Animals

Species	Primary Treatment	Alternative Treatment
Humans: ehrlichiosis and anaplasmosis	Doxycycline 100 mg PO/IV bid × 7-14 days (not during pregnancy) Children should receive doxycycline per standard guidelines During pregnancy, consider treatment with rifampin[19]	Tetracycline 500 mg PO qid × 7-14 days (not for children or during pregnancy)[19]
Dogs, cats	Doxycycline 5 mg/kg PO q12h *or* 10 mg/kg PO q24h × 28 days (give IV for 5 days if the dog is vomiting)	Imidocarb dipropionate 5 mg/kg IM for 2 doses 14 days apart[15,20] *or* oxytetracycline and tetracycline 22 mg/kg PO q8h × 28 days
Horses	Oxytetracycline 7 mg/kg IV SID × 8 days	

Treatment in Animals

Antibiotics and supportive care are the mainstay of clinical disease in dogs and horses. Antibiotics commonly used in small animals include doxycycline, chloramphenicol, and imidocarb dipropionate. Oxytetracycline can be very effective in reducing the severity of illness in cattle.[18] Adjunctive steroid treatment is sometimes used when thrombocytopenia is life threatening. The prognosis is excellent with acute disease and prompt treatment. Prognosis is poor for dogs with *E. canis* infection that progresses to hypoplastic marrow; anabolic steroids may be needed to stimulate bone marrow production. In ruminants, administration of oxytetracycline early in the course of the disease may be beneficial. Tick and infection control strategies are considered effective herd health strategies to prevent clinical cases.[18] Previous infection can produce immunity in horses for several years.[10]

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ESCHERICHIA COLI **INFECTION**

Peter M. Rabinowitz and Lisa A. Conti

Escherichia coli *infection (ICD-10 A04.0-A04.4)*

Other names in humans: E. coli *O157:H7, hemorrhagic colitis*

Other names in animals: colibacillosis

The gram-negative bacterium *Escherichia coli* has hundreds of different strains. These strains can be separated into three categories: (1) nonpathogenic, existing as commensal organisms in the normal gut flora; (2) intestinal pathogenic, causing diarrhea in humans, including enterohemorrhagic *E. coli* (EHEC); enterotoxigenic *E. coli* (ETEC); enteroinvasive *E. coli* (EIEC), enteropathogenic, enteroaggregative, and diffuse-adherent[1]; and (3) capable of causing extraintestinal pathologenic *E. coli* (ExPEC). Case reports have linked enteropathogenic *E. coli* causing canine enteritis in a dog to colonization in a child,[2] an outbreak of necrotizing pneumonia in cats to a strain of ExPEC with molecular features resembling human strains,[3] and cases of edema in pigs tied to toxin-producing strains resembling those occurring in humans.[4] Urinary tract infections in humans have been linked with *E. coli* from food sources.[5] It is likely that additional patterns of interspecies transmission of *E. coli* infection will be recognized in the future[6]; however, this chapter emphasizes current knowledge regarding enterohemorrhagic strains, such as O157:H7. Pathogenic *E. coli* strains, particularly those that are antibiotic resistant, from the food supply are a public health and economic concern.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Ensure that health professionals know how to report cases to the local health authorities.
- Exclude infectious patients from child care or patient care facilities and food production facilities.
- Educate the public on modes of transmission and the preventive measures that they can use, including the following:
  - Discourage consumption of undercooked ground meat and unpasteurized dairy products or juices.
  - Encourage washing raw fruits and vegetables before consumption.
- Monitor the chlorination of public water supplies and pools.
- Identify the source of an outbreak and institute control measures to prevent transmission, including transmission by contaminated food, direct animal contact, or person-person transmission.
- Institute environmental cleanup of contaminated areas. The organism can be maintained in the environment for months in feces and soil. Disinfection agents include 1% sodium hypochlorite, 70% ethanol, and iodine-based solutions.[7]
- Ensure that local petting zoos and other areas where the public has contact with animals have policies and procedures in place to reduce the risk of infection. This includes providing access to handwashing stations, proper manure disposal, and separation of animals from food areas.
- Provide descriptive epidemiology of disease in local human and animal populations.
- Coordinate with agriculture officials to ensure that food safety and farm safety measures are in place.

Human Health Clinicians

- Ensure adequate hydration and consider hospitalization to reduce the risk of hemolytic uremic syndrome.[1]
- Report cases immediately to local health authorities.
- Institute enteric precautions for patients.
- Educate patients about personal hygiene and proper handwashing techniques.
- Avoid the use of antibiotics in patients with Shiga toxin–producing *E. coli* infections.

Veterinary Clinicians

- Counsel animal handlers about hygiene, handwashing, and avoiding direct contact with feces.
- Prevent infection in puppies and kittens by cleaning and disinfecting the parturition environment (1:32 dilution of bleach), ensuring adequate colostrum intake, ensuing that the bitch/queen is in good health, and washing hands/changing clothes and shoes before handling neonates.
- Counsel pet owners to avoid feeding raw or undercooked meat to dogs and cats.

Agent

E. coli is a gram-negative bacillus that is a lactose fermenter and a normal inhabitant of the intestinal tract of most mammals (Figure 9-51). The classification into different serogroups is based on the O polysaccharide antigen. Further differentiation into serotypes is based on the H (flagellar) antigen.[8] The most common serotype of EHEC in human infections is O157:H7. This serotype does not ferment sorbitol, so this aids in the identification of the organism. EHEC organisms are capable of producing potent cytotoxins known as *Shiga toxins 1 and 2* (also known as verocytotoxins). Shiga toxin 1 is also produced by *Shigella dysenteriae* (see Chapter 11).

Geographical Occurrence

EHEC strains have been identified in North America and South America, Europe, Japan, and southern Africa. The distribution of these strains in other parts of the world is unknown.[1]
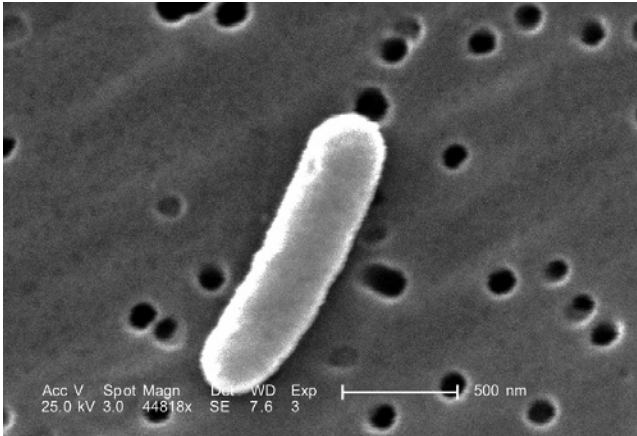
Figure 9-51 ▪ At an extremely high magnification (×44,818), this scanning electron micrograph revealed some of the morphologic details displayed by a single gram-negative *Escherichia coli* bacterium. This bacterium was a member of the strain O:169 H41 ETEC (enterotoxigenic *E. coli*). (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy J.H. Carr.)

Groups at Risk

Although *E. coli* infections can occur in persons of all ages, children younger than 5 years are at increased risk of developing serious complications from EHEC infections, including hemolytic uremic syndrome (HUS). In the elderly, thrombocytopenic purpura may develop.

Hosts, Reservoir Species, Vectors

Cattle are the principal reservoir for EHEC. Other ruminants may also be reservoirs. EHEC strains have been identified in sheep, goats, turkeys, chickens, cats, deer, swine, horses, and dogs.[9,10] Contaminated meat and other food are major vehicles for human infection. Human-to-human transmission is common. When a subclinically infected cat was found to have the same strain of O145:H-EHEC as a child with bloody diarrhea, it was not possible to determine the direction of the transmission, so human-to-animal transmission may be possible as well.[11]

Mode of Transmission and Life Cycle

Transmission occurs through direct contact with feces or through the ingestion of meat, dairy products, produce, or water that is contaminated with feces (Figure 9-52). The infective dose is estimated to be fewer than 10 organisms.[12] Subclinically infected animals may shed organisms in their feces for prolonged periods.

Significant outbreaks have been linked to contaminated beef, vegetables and fruit, and unpasteurized juice and dairy products. Contaminated dust settling into drinks has been suspected in outbreaks associated with fairs and petting zoos. Contaminated swimming pools and drinking water supplies have been associated with waterborne transmission of the bacterium.[13] After the organisms have been ingested, they reproduce in the intestinal tract. The incubation period to clinical illness is between 2 to 10 days.[1] Infected humans may then shed organisms in their feces for several weeks.

Shiga toxin–producing *E. coli* result in cytotoxic effects on intestinal epithelia that cause characteristic bloody diarrhea. Shiga toxins systemically cause renal endothelial damage and possible HUS.

Environmental Risk Factors

E. coli has been shown to persist in contaminated environments for prolonged periods.[14] The organism may persist for longer periods in the soil in cold climates.

Forty-two weeks after an outbreak of human illness at a fair in Ohio, *E. coli* O157:H7 was able to be recovered from the sawdust in the implicated barn.[15] Campers have become infected by camping and contacting mud and soil in pastures where livestock such as sheep have grazed in the past.[12]

Disease in Humans

E. coli O157:H7 and other EHEC strains of *E. coli* cause varying infections that can range from asymptomatic to fatal. Common symptoms include watery diarrhea, often (in more than half of cases[16]) followed by large amounts of blood, abdominal cramping, and colitis (Color Plate 9-29). Fever is either low grade or absent.
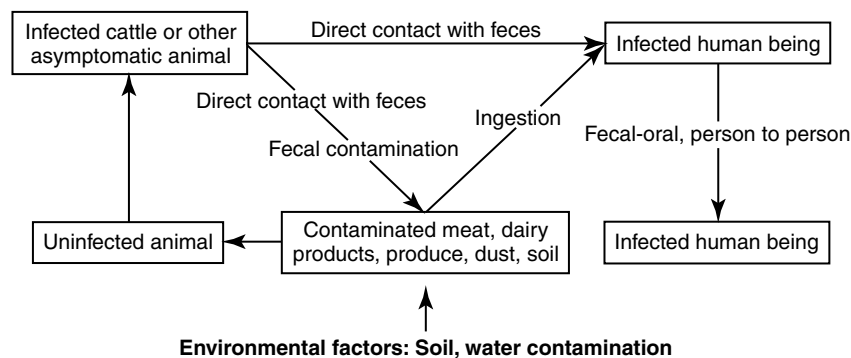

Figure 9-52 ▪ Life cycle of *E. coli* O157:H7 infection.

In most cases, the disease can resolve in 5 to 10 days without antibiotics.[17] Severe complications are more common in children and the elderly and include HUS in approximately 10% of cases, acute renal failure, coagulopathies, and anemia.[18] *E. coli* O157:H7 is the major cause of HUS in the United States and the most common cause of acute renal failure in children.

Disease in Animals

Cattle are typically subclinical carriers for *E. coli* O157:H7 (Figure 9-53). Herd prevalence rates in excess of 40% have been reported. Studies of calves have shown EHEC prevalence rates of almost 70%.[19] Sheep (rates in excess of 30%), dogs, deer, swine, and other animals may also subclinically carry EHEC.

ETC, EPEC, uropathogenic *E. coli*, and cytotoxic necrotizing factor *E. coli* have been recovered from dogs, while EPEC, VTEC, and uropathogenic *E. coli* organisms have been recovered from cats. Many of the *E. coli* strains that have been recovered from dogs and cats are hemolytic.

Neonates that have not had adequate amounts of colostrum are more susceptible to enteritis or septicemia caused by β-hemolytic *E. coli*. Sporadic cases of *E. coli* enteritis, cystitis, endometritis, pyelonephritis, prostatitis, or mastitis have also been reported in puppies and kittens, as well as

Figure 9-53 ■ Cattle are typically subclinical carriers of *E. coli*. (From Divers TJ, Peek SF (eds): *Rebhun's diseases of dairy cattle*, ed 2, St Louis, 2008, Saunders Elsevier. Courtesy Robert O. Gilbert.)

adult dogs and cats. Table 9-30 compares clinical presentations of *E. coli* infection (enterohemorrhagic) in humans and other animals.

Diagnosis

Fecal samples should be cultured on sorbitol/MacConkey's media. All EHEC strains should be sent to a public health laboratory for serotyping to characterize the strain and detect possible outbreaks. There are also commercial assays for Shiga toxins and DNA probe for specific genes.[1] Subtyping of *E. coli* O157:H7 can be done using pulsed gel electrophoresis to further detect outbreaks.

Treatment

Many human cases of EHEC infection are self-limiting and do not require medical intervention. Even in more serious cases, it is believed that antibiotic treatment and antimotility agents may increase the release of toxins and increase the risk of HUS.[16] Supportive measures include fluid and electrolyte replacement and monitoring of hematologic and renal function for the development of HUS. HUS often requires transfusion, dialysis, and intensive care.[20]

In adult animals the disease may be self-limiting; however, animals with clinical signs may need intensive supportive care. Antibiotic therapy protocols should be based on culture results and sensitivity testing. Trimethoprim-sulfa can be used at 30 mg/kg orally every 12 to 24 hours or amoxicillin can be used at 10 to 20 mg/kg orally every 8 to 12 hours. The prognosis for neonates with clinical signs is often poor.

WEB RESOURCES

- Diagnosis and Management of Foodborne Illnesses: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5304a1.htm
- *E. coli* Resources for Clinicians: http://www.cdc.gov/ecoli/clinicians.htm

Table 9-30 ■ *E. coli* (Enterohemorrhagic): Comparative Clinical Presentations in Humans and Other Animals				
Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans	Children; crowding; contact with feces; consumption of undercooked meat or unpasteurized milk, cider, or juice; ingestion of water from lakes and pools while swimming	2-10 days	Watery diarrhea, bloody diarrhea, abdominal cramping	Positive fecal culture
			HUS, renal failure	Leukocytosis, anemia, thrombocytopenia, abnormal renal function tests
Cattle, poultry, deer, swine	Neonates with inadequate colostrum/immune system		Subclinical carriage; neonates with diarrhea, dehydration, and depression; hypovolemic shock	Positive fecal culture
Dogs, cats	Neonates, inadequate colostrum intake		Subclinical carrier, diarrhea	Positive fecal culture, cytotoxin assays

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GIARDIASIS

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Giardiasis (ICD-10 A07.1)

Other names in humans: lambliasis, backpacker's disease, beaver fever, traveler's diarrhea

Other names in animals: giardosis, lambliasis, lambliosis

Giardia intestinalis (also known as *Giardia lamblia*, *Lamblia intestinalis*, *Giardia duodenalis*)[1] is a common parasitic cause of infectious diarrhea in humans. Human cases are thought to be a result of person-to-person transmission, either directly or through contaminated water supplies. The importance of animals, including dogs and cats, as disease reservoirs and sources of zoonotic transmission of the disease remains incompletely understood and potentially overlooked by human health clinicians and public health authorities. Recent advances in molecular genotyping hold promise for clarifying the risk of *Giardia* infection related to human-animal contact.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Disease is reportable to public health authorities in some states.
- Ensure public water supplies are not contaminated with human or other animal waste and that water treatment includes filtration.
- In the event of a case report, determine risk factors for infection and whether others are at risk.
- Consider zoonotic sources of infection (e.g., pets, farm animals/petting zoos, water supplies with animal contact).
- Educate the public, veterinarians, and human health clinicians about risk factors for transmission, including not drinking untreated surface water.
- Support policies to clean up dog feces and other animal waste in public areas.
- Ensure that day care center staff have proper training to avoid outbreaks.

Human Health Clinicians

- Check with your state health office to determine whether the disease is reportable to public health authorities using the case definition; see http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5607a2.htm.
- Include questions about animal contact in every patient presenting with diarrhea. If pets are in the house, suggest a consultation with the family veterinarian. Human *Giardia* may be able to infect pets.
- Person-to-person transmission is possible. Counsel infected persons about handwashing, avoiding swimming for 2 weeks after symptoms end, and avoiding fecal exposure during sexual activity.

- Counsel owners and any others in contact with infected animals about the zoonotic risk, need for handwashing after handling pet, feces, pet toys, and other objects that are potentially infected or contaminated with cysts.
- Decontaminate infected animal's coat with shampoo; also decontaminate kennels or other environments with quaternary ammonium disinfectants that are effective in inactivating *Giardia* cysts.
- Consider vaccinating puppies and kittens at 7 weeks, with booster 3 weeks later, against *Giardia* trophozoites[1] (controversial).
- Decontaminate hard surfaces with 1% sodium hypochlorite, 2% glutaraldehyde, or quaternary ammonium solutions.[1]
- Keep pets indoors to reduce their exposure to the organism.

Agent

Giardia is a genus of flagellated protozoan parasite that lives principally in the upper intestine of vertebrates (Figure 9-54). Recent classification identifies *Giardia intestinalis* as the major species responsible for human infection. *Giardia* species are found in most mammals, and while different strains appear to have adapted to specific host species, molecular tools for typing particular isolates are now allowing an examination of how much zoonotic transmission is taking place. The current classification includes at least seven distinct assemblages (genotypes) of *G. intestinalis*: A and B are found in humans and a number of other animals, and C through G appear to be more host specific.[2,3] *Giardia* organisms exist in two forms, a vegetative trophozoite form capable of causing illness in the host, and a transmissible cyst form that is shed in feces (Figure 9-55). The cysts measure 7 to 10 microns by 8 to 13 microns and can survive up to 2 months in water, where they are resistant to routine chlorination. Upon ingestion by a host, the cysts develop into pathogenic trophozoites that cling to the brush border surface of the intestinal mucosa and reproduce by fission.
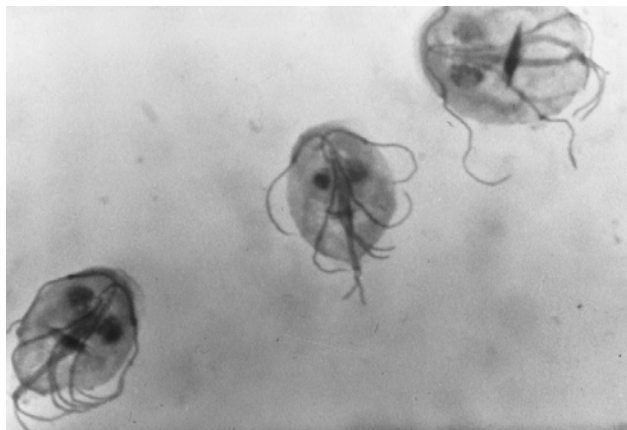
Figure 9-54 ■ Wet mount of a fresh fecal sample showing motile trophozoites of *Giardia* species. Notice the prominent pair of nuclei containing a single karyosome of condensed chromatin, flagella running longitudinally between the nuclei, and a pair of curved median bodies. The arrangement of the organelles resembles a wide-eyed face. (From Quesenberry K, Carpenter JW: *Ferrets, rabbits and rodents: clinical medicine and surgery*, ed 2, St Louis, 2004, Saunders Elsevier.)
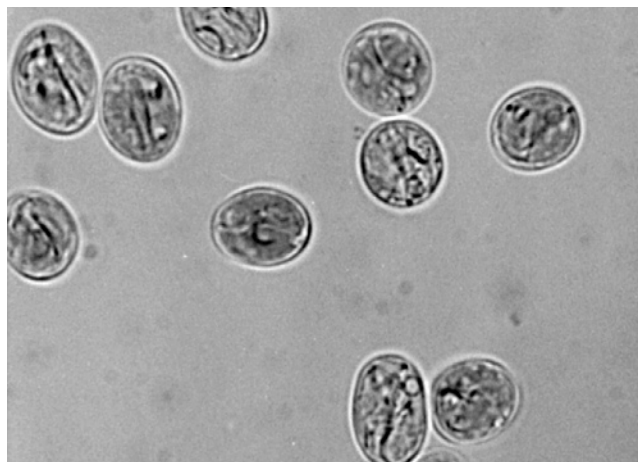
Figure 9-55 ■ *Giardia* cysts concentrated from the feces of a cat by the zinc sulfate centrifugal flotation technique. Cyst wall, nuclei, axonemes, and median bodies are apparent in several of the cysts (iodine, ×1100). (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier.)

Geographical Occurrence

G. intestinalis occurs worldwide in humans and other animals, with greater human prevalence in regions with poor sanitation practices and crowding. Reported prevalence in human populations ranges from 2% to 4% in developed countries to more than 15% in children from developing countries.

Groups at Risk

Children appear to become infected more frequently than adults. Particular risk groups include children in day care facilities, day care workers, parents of infected children, individuals living in areas without adequate sanitation or who drink from shallow wells, wilderness travelers who drink unfiltered or untreated water, swimmers who swallow water from lakes or ponds, international travelers, and men who have sex with men.[4]

Hosts, Reservoir Species, Vectors

In many host species, *Giardia* infection can produce humoral immunity after 100 days that may result in self-limiting infection.[5] In the United States, the prevalence of *Giardia* in canine kennels has been reported up to 100%.[6] Humans and a wide range of other animals are reservoirs. In many individuals and species, asymptomatic carriage may occur with the ability to transmit the infection to others.

Studies of infection prevalence in animals vary greatly: 20% to 35% in puppies, 10% to 15% in kittens, 5% to 90% in calves, 60% to 80% in lambs, 17% to 32% in foals, and 7% to 44% in young pigs.[7]

Mode of Transmission and Life Cycle

Cysts develop in the intestine and are shed into the environment in feces, where they are immediately infective (Figure 9-56). Transmission occurs when cysts are ingested through drinking water, direct fecal-oral contamination,
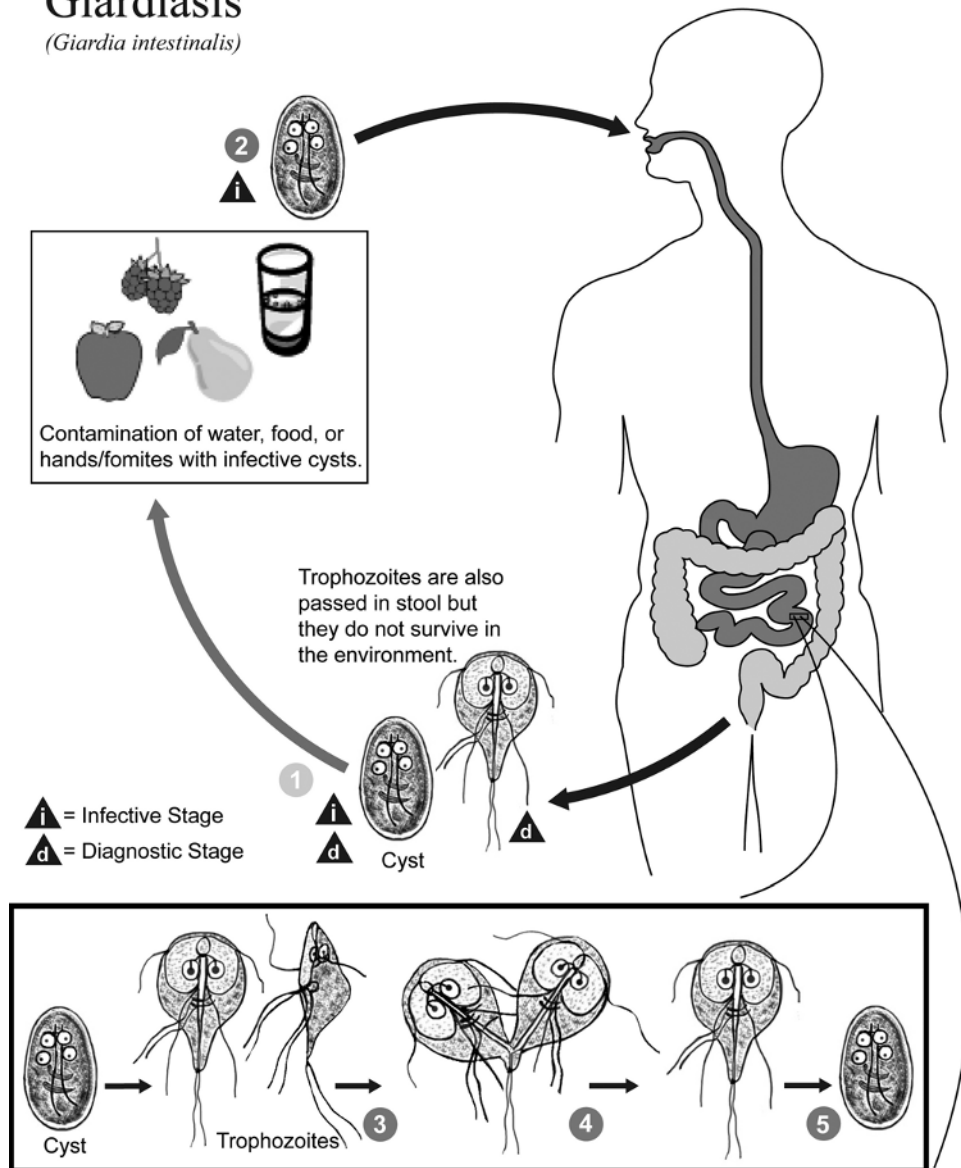
Giardiasis
(Giardia intestinalis)

Figure 9-56 ■ Life cycle, giardiasis. Cysts are resistant forms and are responsible for transmission of giardiasis. Both cysts and trophozoites can be found in the feces (diagnostic stages). *1,* The cysts are hardy and can survive several months in cold water. Infection occurs by the ingestion of cysts in contaminated water, food, or by the fecal-oral route (hands or fomites). *2,* In the small intestine, excystation releases trophozoites (each cyst produces two trophozoites). *3,* Trophozoites multiply by longitudinal binary fission, remaining in the lumen of the proximal small bowel where they can be free or attached to the mucosa by a ventral sucking disk. *4,* Encystation occurs as the parasites transit toward the colon. The cyst is the stage found most commonly in nondiarrheal feces. *5,* Because the cysts are infectious when passed in the feces or shortly afterward, person-to-person transmission is possible. While animals are infected with *Giardia*, their importance as a reservoir is unclear. (From Centers for Disease Control and Prevention: *Giardiasis.* http://www.dpd.cdc.gov/dpdx/HTML/Giardiasis.htm. Accessed September 13, 2008.)

foodborne exposure, or contact with contaminated objects leading to ingestion. Infected drinking water is thought to be the major form of transmission. The infective dose is low, with a median infective dose (ID_{50}) of 10 cysts. Fecal excretion is high—an infected human can secrete 900 million cysts per day.[8]

Once the cysts are ingested, they develop into trophozoites in the small intestine. The trophozoites remain there and, if they cause disease, they do so without invading the mucosa. They have a sucking disk by which they attach to the entero-cytes and are thus not shed continuously. Reproduction takes place by binary fission and cysts are produced to continue the life cycle.

Circumstantial evidence, such as finding similar genotypes in both children and household dogs, suggests that transmission between pets and people takes place.[9,10] Case control studies have shown increased odds for infection among pet owners and people reporting contact with farm animals.[11] Transmission in animals, as in humans, occurs through ingestion of cysts.

Environmental Risk Factors

Because the *Giardia* cyst can persist for months in the environment, the status of water supplies is a critical environmental factor in sporadic and epidemic outbreaks of giardiasis in both humans and animals. Inadequate filtration of drinking water supplies has been associated with major outbreaks. The degree of contamination of municipal water supplies and shallow wells with animal and human feces is also important. On farms, contamination of water sources could spread infection among animals.

Dogs shedding cysts in feces can contaminate environments such as a lawn or public park for months,[12–14] leading to risks to children who play around soil. Similarly, livestock housing facilities and grazing areas can become contaminated with *Giardia* cysts, leading to infection risk for animals and farmers. Even marine shellfish are capable of being contaminated with *Giardia* cysts, suggesting a foodborne infection risk to humans.[15]

Disease in Humans

Giardia infection in humans is usually asymptomatic or mild enough to escape diagnosis. Most cases are self-limited, yet significant acute and chronic infection can occur. Acute infection can produce bloating, abdominal pain, explosive diarrhea, with pale, frothy, steatorrheic feces often mixed with mucus, but not blood. Symptoms may be continuous or intermittent (with bouts of constipation).

In chronic infections, there can be bloating, abdominal pain, flatulence, steatorrhea, lactose intolerance, and weight loss. In children this can lead to failure to thrive and developmental delays.[16] Rarely, infection can lead to reactive arthritis.

Disease in Animals

In dogs and cats, the disease is often subclinical. Young animals are more likely to show signs of infection and present with frothy diarrhea that may be foul smelling. Calves, lambs, foals, and caged birds (cockatiels, parrots) may also develop diarrhea due to *Giardia*. Table 9-31 provides a comparison of clinical manifestations of giardiasis.

Diagnosis

In humans, the differential diagnosis includes other causes of chronic diarrhea, including bacteria such as *Campylobacter*
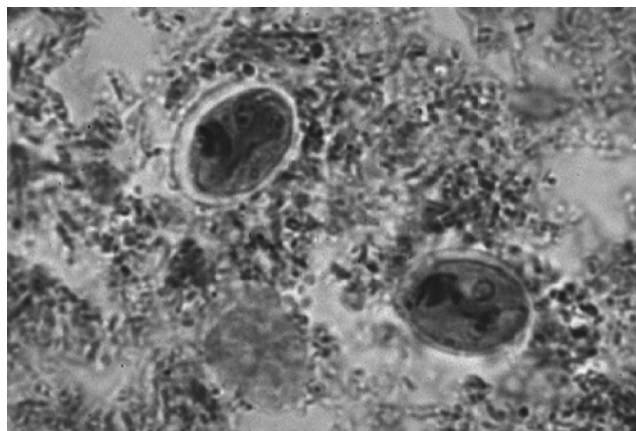
Figure 9-57 ▪ *Giardia lamblia* in a reptile. (From Mader DR: *Reptile medicine and surgery*, ed 2, St Louis, 2006, Saunders Elsevier. Photograph courtesy F.L. Frye.)

and *Salmonella*, viral gastroenteritis, and other protozoa including *Cryptosporidium* and *Cyclospora,* and underlying disease such as celiac sprue. Diagnosis is typically by direct microscopic visualization of trophozoites or *Giardia* cysts in the feces. Repeated fecal analysis may be necessary. ELISA and IFA tests for antigen are also commercially available. It should be noted that demonstration of cysts alone in feces does not prove *Giardia* is the cause of a diarrheal episode because many *Giardia* infections are asymptomatic. In questionable cases, a duodenal aspirate, string test, or biopsy may be performed to detect trophozoites.[18]

Animal diagnosis involves testing for *Giardia* trophozoites in direct unstained fecal smears to look for motile trophozoites or using Lugol's iodine to help distinguish the cysts and trophozoites (Figure 9-57).[19] A zinc sulfur concentration test (ZCST) is a fecal flotation method for cysts and is considered a more sensitive test than a newer, fecal ELISA. A direct IFA test may be more sensitive for detecting low numbers of cysts.[20]

Treatment

Acute giardiasis is treated with supportive care including rehydration. Antibiotics are indicated for symptomatic patients. Table 9-32 provides treatment information for giardiasis in humans and other animals.

All drugs for *Giardia* treatment are extralabel in animals. However, a number of drugs are effective. In addition to antibiotic treatment, an animal's coat should be washed

Table 9-31 ▪ Giardiasis: Comparative Clinical Presentations in Humans and Other Animals			
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**
Humans	Children, day care centers, areas of poor sanitation, international travel, backpackers, pet ownership, farm animal contact	3-25 days[17]	Asymptomatic *or* acute diarrhea with bloating, chronic diarrhea with malabsorption, weight loss
Dogs, cats, calves, rodents, reptiles	Crowding, contaminated environments	5-14 days	Often subclinical
	Young animals at increased risk of clinical disease		Weight loss, intermittent diarrhea; chronic infection can lead to debilitation

Table 9-32 ▪ Antibiotic Treatment of *Giardia* Infection in Humans and Other Animals		
Species	**Primary Treatment**	**Alternative Treatment**
Humans	Tinidazole 2 gm PO × 1 *or* nitazoxanide 500 mg PO bid × 3 days	Metronidazole 250 mg PO tid × 5 days If pregnant: paromomycin 500 mg 4×/day × 7 days[21]
Dogs, cats[22]	Fenbendazole 50 mg/kg PO q24h × 3-5 days; a second 5-day course may be necessary	Albendazole 25 mg/kg PO q12h for 2 days; a second 5-day course may be necessary
Cattle	Fenbendazole 5-10 mg/kg PO × 3 days	Albendazole 20 mg/kg 1 PO once daily for 3 days

with an antiseptic shampoo solution to eliminate cysts. Vaccines[19] have been developed for dogs and cats, but their use is controversial.

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HANTAVIRUS INFECTIONS

Peter M. Rabinowitz and Lisa A. Conti

Hantavirus pulmonary syndrome (ICD-10 A), hemorrhagic fever with nephropathy (ICD-10 A)

Other names in humans: hantavirus (cardio-) pulmonary syndrome (HPS); Four-corners' disease; in western Europe, nephropathia epidemica; in parts of eastern Europe and Asia, hemorrhagic fever with renal syndrome (Korean hemorrhagic fever); also many local names

Other names in animals: none

Clinical syndromes of hantavirus infection, including hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with nephropathy, are thought at present to be principally human diseases. However, the presence of domestic animals in, and wildlife around, a household can increase the risk for rodent infestation or contact that can result in hantavirus risk to humans. Limiting contact between humans and rodents (including wild species and laboratory animals) can reduce the risk of infection. However, these interventions are unlikely to prevent sporadic transmission with serious fatal outcomes.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide descriptive epidemiology of cases in the health district.
- Educate the public about measures to reduce risk, including the following:
  - Controlling rodents and their fleas near dwellings (flea control should precede rodent control to

prevent fleas from seeking new hosts): Box 9-4 lists steps for rodent proofing homes
  ○ Avoiding camping near rodent burrows
  ○ Avoiding handling wild rodents[1]
- Provide exposure risk reduction guidance to workers with occupational risk (see below).

Human Health Clinicians

- Report disease to public health authorities using the case definition (All About Hantaviruses): http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/phys/casedefn.htm.
- Ensure that workers in affected areas who are frequently exposed to rodents or who are involved in cleanup of rodent-infested areas are informed of their occupational risk and have a baseline medical screening, including respirator fit testing. They should use protective equipment—including either half-face or supplied air respirators with N100 or P100 filters (Color Plate 9-30)—and gloves while handling rodents or traps containing rodents; they also should disinfect gloves after use.[2,3]
- If fever or respiratory symptoms develop in a worker within 45 days of the last potential exposure, he or she should immediately seek medical attention and inform the health care provider of the potential occupational risk of hantavirus infection. The provider should contact local public health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be submitted to the state health department for hantavirus antibody testing.[4]

Veterinary Clinicians

- Counsel clients about pet-feeding practices that reduce the risk of rodent infestation.
- Dogs and cats are not known to be infected with hantaviruses, but these pets may bring infected rodents into contact with people.
- Train veterinary personnel in biosafety measures to reduce risk from infected rodents.

Agent

Hantaviruses are trisegmented, negative-sense RNA viruses in the Bunyaviridae family. Unlike other bunyaviruses, which are arthropod borne, hantaviruses are rodent borne. A number of species cause human disease, and new hantaviruses and their rodent hosts continue to be described. Like other segmented RNA viruses, hantaviruses appear capable of reassortment when dual infections of target cells occurs, which could lead to the emergence of novel strains.[5]

Geographical Occurrence

In the New World, hantaviruses are found from Canada to Argentina. In North America, Sin Nombre, New York-1, Bayou, and Black Creek Canal hantaviruses have been associated with HPS.[6] In South America, HPS caused by Andes virus may be particularly pathogenic for humans, and rare occurrence of human-human transmission of infection has been linked to this virus in Argentina.[7,8] Old World members of the family, including Seoul virus, Hantaan virus, and Dobrava-Belgrade virus, cause hantavirus hemorrhagic fever with renal syndrome.[9] Another Old World virus, Pumaala virus, causes a somewhat milder disease generally referred to as *nephropathia epidemica.* Pumaala virus is the predominant hantavirus in western and central Europe, whereas Hantaan and Dobrava-Belgrade viruses are found in eastern Europe. Hantaan virus is the major pathogen in Asia and has also been detected in Africa.

Groups at Risk

In the United States, groups at increased risk for hantavirus infection are those with rodent contact, including persons living in endemic areas such as the Southwest, forestry workers, farm workers, construction workers engaged in renovation, wildlife biologists and zoologists, and laboratory animal handlers. Although the risk to such groups is low overall, it may be higher in areas of endemic foci.[2]

Hosts, Reservoir Species, Vectors

Rodents and, in a few instances, insectivores (shrews) are the reservoir host of hantaviruses, and each hantavirus species is associated primarily with a single rodent or insectivore species.[10] Hantavirus infection within individual rodents of a reservoir species is believed to occur horizontally, with males frequently infected at higher prevalence than females.[4] Lifelong persistence of infection with sporadic shedding of virus has been demonstrated for multiple species. HPS is associated with rodents of the subfamily Sigmodontinae.
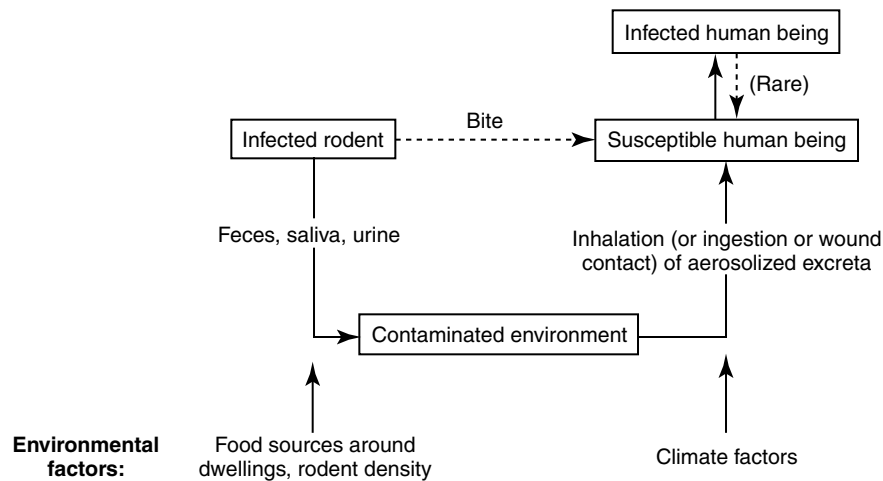
Figure 9-58 ▪ Transmission of hantavirus infection.

The principal reservoir for hantavirus in the United States is the deer mouse (*Peromyscus maniculatus*, Color Plate 9-31); other rodents carriers are the cotton rat (*Sigmodon hispidus*), the rice rat (*Oryzomys palustris*), and the white-footed mouse (*Peromyscus leucopus*). Seoul viruses are carried by rats (*Rattus* species).[11] Although most of these reservoir species are usually found in more rural areas, they are capable of infesting buildings in periurban zones near forested areas.[12]

Mode of Transmission and Life Cycle

The spread of virus to humans is believed to occur primarily through inhalation of aerosol of dried feces, saliva, or urine from infected rodents (Figure 9-58). Bites from infected rodents or contact with their feces, saliva, or urine with broken skin, mucous membranes, or through ingestion are other possible transmission pathways.

Person-to-person transmission has been reported only for Andes virus, which has been isolated from human saliva[13]; this transmission required close personal contact in an enclosed space (bus).[8]

Environmental Risk Factors

Contamination of the environment by urine, saliva, and feces of infected rodents is the principal driver of transmission. Under certain conditions, the virus can persist for prolonged periods (several months) in the environment.[14]

Environmental factors that increase the density of rodents around human habitation are critical to human risk. These factors include abundance of food sources (unsecured food in kitchens, seeds from bird feeders, pet/livestock food). A combination of mild winters and increased rainfall related to El Niño cycles has also been associated with increased rodent abundance.[15]

Spatial risk mapping in the American Southwest has identified areas of increased hantaviral transmission related to elevation and precipitation.[16]

Disease in Humans

Hantavirus Pulmonary Syndrome

HPS is a life-threatening disease that begins with a nonspecific prodrome of fever, chills, and myalgia, leading to hypotension and pulmonary edema with accompanying respiratory distress and shock. The incubation period is 1 to 4 weeks.

Radiographs may reveal diffuse alveolar infiltrates (Figure 9-59). Mechanical ventilation is often necessary. Complications may include disseminated intravascular coagulation, myocardial dysfunction, and cardiac arrhythmias. The case fatality rate may reach 40%. In parts of South America, however, milder forms of the disease may occur.[17]

Hantavirus Hemorrhagic Fever with Nephropathy (Hemorrhagic Fever With Renal Syndrome)

This is a disease of variable severity, with a number of different clinical stages.[11]

Figure 9-59 ▪ Pulmonary infiltrates in hantavirus pulmonary syndrome. (From Centers for Disease Control and Prevention: *Severe hantavirus pulmonary syndrome.* http://www.bt.cdc.gov/agent/plague/trainingmodule/3/12hantavirus.htm. Accessed October 2008.)

1. The *febrile* or *toxic* stage is characterized by the abrupt onset of fever, chills, and headache that may be accompanied by photophobia and other symptoms.
2. The *hypotensive* phase may involve clinical shock and death.
3. The *oliguric* (renal) phase follows the hypotensive phase and includes declining renal function and urine output. Hemorrhagic complications may occur.
4. The *diuretic* phase is characterized by improved urine output and clinical condition.
5. The *convalescent* phase may include long-term abnormalities of renal function, including renal acidosis and renal insufficiency.

Disease in Animals

Rodents appear to have subclinical infection with hantaviruses. Serological studies in the United States have failed to demonstrate significant rates of subclinical infection in dogs or cats.[18]

Diagnosis

The differential diagnosis includes legionella, plague, tularemia, Q fever, leptospirosis, Goodpasture's syndrome (antiglomerular basement antibody disease), and drug-induced noncardiac edema. Typical hematologic findings of hantavirus infection include immature neutrophils (bandemia), atypical lymphocytosis, and thrombocytopenia.[19] An ELISA IgM test is available, and immunohistochemistry can be used for retrospective diagnosis.

Treatment

There is no specific treatment for HPS. Treatment is supportive. Clinicians need to have a high suspicion for the disease because patients require early transfer to an intensive care unit. Mechanical ventilation and support of blood pressure with pressor agents may be necessary. Extracorporeal membrane oxygenation has reportedly provided clinical benefit in some cases.

Hantavirus hemorrhagic fever with nephropathy is also treated with supportive measures, including dialysis if necessary. Ribavirin has been used in some cases.[17]

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HOOKWORM INFECTION

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Cutaneous larva migrans (ICD-10 B76.9) Disease due to Ancylostoma caninum ***or*** Ancylostoma braziliense *(B76.0)*

Other names in humans: ancylostomiasis, creeping eruption, ground itch, dew itch, sandworm, cutaneous larva migrans

Other names in animals: ancylostomiasis

Hookworms of the genus *Ancylostoma* are common parasites that can cause serious infections in dogs and cats and usually milder illness in humans. The classic manifestation of *A. caninum* and *A. braziliense* infection in humans is a dermatitis resulting from the larvae burrowing under the skin, known as *creeping eruption* or *cutaneous larva migrans*. Preventive veterinary care and healthy public policies about pet sanitation can reduce the risk of human disease.

Public Health Professionals

- Restrict dogs and cats from beaches and other recreational areas or require cleanup of all animal feces.
- Promote strategic deworming of all pets.
- Educate the public about risk of unprotected contact with sand and soil (e.g., need to wear shoes while walking on beach, using a waterproof barrier to damp soils when working under a house).
- Recommend rodent control as rodents are paratenic hosts (intermediate hosts are not needed for parasite development).

Human Health Clinicians

- Counsel patients in endemic areas and travelers to endemic areas about the risks of unprotected skin contact to soil and sand.
- Counsel patients about handwashing after handling potentially contaminated soil, washing vegetables and fruit.

Veterinary Clinicians

- Provide strategic deworming to dogs and cats.
- Counsel clients to keep dogs on leash and properly dispose of feces, discourage contact with wildlife, keep cats indoors.
- Treat pregnant bitches prophylactically.
- Decontaminate soil and lawns with sodium borate.

Agent

Hookworms are nematode worms (Color Plate 9-32). Although a number of hookworm species occur in humans and other animals, *A. canium* (dog hookworm) and *A. braziliense* are the species associated with human disease in the United States. *A. braziliense* is considered the most common cause of cutaneous larva migrans.[1] A related species, *A. ceylanicum*, has historically been confused with *A. braziliense*.[2] The adult *A. caninum* worms are 12 to 15 cm in length; the other species are somewhat smaller.

Geographical Occurrence

Because the larvae prefer warm, humid environmental conditions, hookworm infection is more common worldwide in tropical and subtropical regions. *A. caninum* is more widely distributed than *A. braziliense* or *A. ceylanicum*. In the United States, infection with *A. caninum* and *A. braziliense* occurs mostly in the southeast states along the Gulf of Mexico. *A. ceylanicum* is found in tropical regions.

Groups at Risk

Exposure to contaminated soil and sand is a major risk factor; therefore human cases occur among bathers who walk barefoot on contaminated beaches or soils. Other risk groups include gardeners, workers who have to crawl into contaminated crawl spaces under buildings, and travelers to tropical regions.

Hosts, Reservoir Species, Vectors

Dogs are the principal reservoir for *A. caninum*. *A. braziliense* occurs in cats and dogs. A survey of feral cats in Florida found 33% infected with *A. braziliense*. *A. braziliense* also is found in wild felids. It is thought that infection in rodents (paratenic hosts) may also play a role in disease transmission.[2]

Mode of Transmission and Life Cycle

Dogs and cats become infected through ingestion of larvae, skin penetration of larvae or from transmission in milk or colostrum of infected bitches (dogs) (Figure 9-60). In puppies and kittens, the larvae migrate through the bloodstream and lymphatics to the lungs, where they are coughed up and swallowed and mature in the small intestine. Approximately 15 to 20 days after infection, the mature worms produce eggs.[3] In older cats and dogs, the life cycle is arrested in the larval stage, but such larvae may become reactivated if adult worms are removed from the intestine or during pregnancy.

After an infected animal sheds eggs into the environment in feces, the eggs complete embryonation, hatch, and larvae begin to develop through a series of stages. The process of developing into infective larvae takes 7 to 10 days in moist, warm soil.[4]

Larvae infect humans through contact with skin, usually of the foot. This produces a characteristic dermatitis (ground itch). The larvae of *A. caninum* and *A. braziliense* burrow under the skin but eventually die. In the process they produce the lesions of cutaneous larva migrans. Larvae of *A. ceylanicum*, however, pass through the lymphatics and bloodstream into the lungs, ascend up the trachea where they are swallowed (similar to infection in dogs and cats), and reach the small intestine, where they attach to the wall and develop to maturity in 3 to 4 weeks.[4]

Environmental Risk Factors

Temperature, humidity, and soil type are important factors determining how well the hookworm eggs hatch and develop into infective larvae. In general, these organisms prefer moist, warm climates and moist, sandy soils. In moist, warm conditions the third-stage (infective) larvae can survive up to 3 weeks.[3] Pet sanitation policies in beaches, parks, and other public places can affect the risk of human infection.

Disease in Humans

Human infection with *A. caninum* or *A. braziliense* causes a linear dermatitis that appears within days to weeks after infection (Color Plate 9-33). The rash is usually accom-
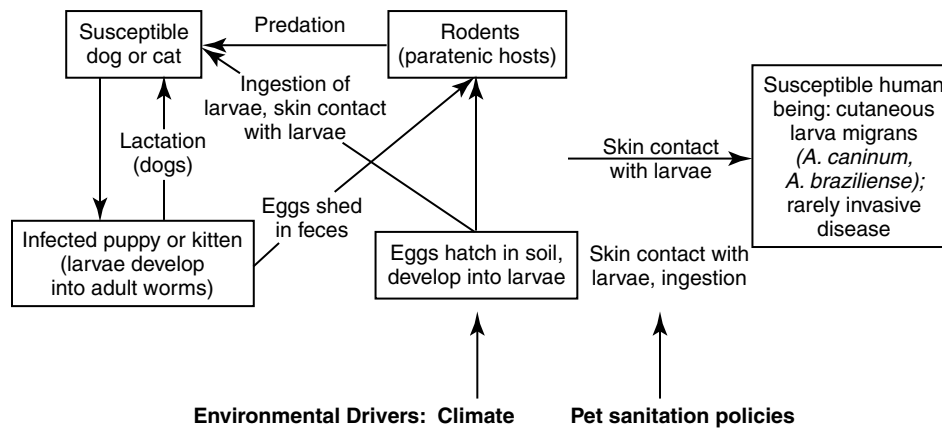
Figure 9-60 ■ Life cycle of hookworm infection.

panied by intense itching, erythema, and edema. Vesicles may appear. Secondary infection may occur. The infection may last weeks or months. Laboratory findings can include eosinophilia and increased IgE levels.

Rarely, cases of intestinal infection with *A. caninum* have occurred. In such cases, larvae migrate deeper and may reach the intestines causing eosinophilic enteritis. Loeffler's syndrome (eosinophilia, asthma, migratory pulmonary infiltrates, fever, and urticaria) has been described.[5]

Disease in Animals

In young animals, hookworm infection can be an acute disease process with significant blood loss and sudden death. Black, tarry stools may occur. Laboratory tests show anemia that may be accompanied by eosinophilia. The fourth larval stage and adult worms cause a chronic anemia and enteritis. The lung migration phase of the life cycle can rarely cause a dry cough.[6] Because animals may repopulate the bowel with larvae dormant in tissues, infection may continue for months or years. Dogs previously sensitized to *Ancylostoma* may manifest "hookworm dermatitis" at sites of percutaneous larval penetration (Color Plate 9-34). Table 9-33 shows the comparative clinical presentation of hookworm infection in humans and other animals.

Diagnosis

Cutaneous larva migrans in humans is diagnosed clinically by the characteristic linear, slow-moving rash and a history of exposure to potentially contaminated soils. Biopsy may show an eosinophilic infiltrate but usually does not reveal the organism and therefore is not generally indicated to establish the diagnosis.[7] In animals, eggs can be identified in feces by fecal flotation (Figure 9-61).[6]
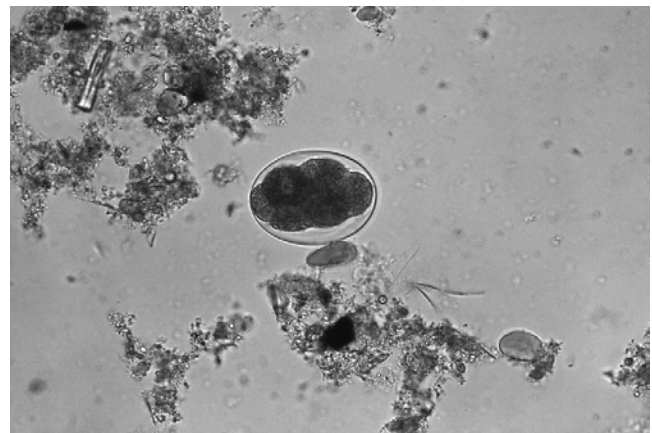

Figure 9-61 ■ Hookworm ova. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

Table 9-33 ■ Hookworm Infection: Comparative Clinical Presentations in Humans and Other Animals				
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**	**Laboratory Findings**
Humans	Unprotected skin contact with soil, sand	Days to weeks	Linear skin eruption with pruritus, erythema, edema *Rarely*: Loeffler's syndrome, eosinophilic enteritis	Eosinophilia
Dogs	Puppies at increased risk of severe disease	Varies with the number of parasites	Anemia, acute or chronic; weight loss; tarry stools; sudden death	Anemia, iron deficiency Eggs in feces
Cats	More severe signs in kittens		Usually subclinical	Anemia (rare), eggs in feces

Treatment

Treatment in Humans

Many human cases of cutaneous larva migrans are self-limited and do not require medical intervention. However, in symptomatic and persistent infection, anthelmintic therapy is warranted. Topical thiabendazole cream may be effective.[7] Table 9-34 lists choices of oral anthelmintic agents, which are associated with a high cure rate.

Treatment in Animals

Acute illness in dogs and cats is treated with an antihelmintic, as well as supportive care such as blood transfusions. In dogs, adult larvae treatment is sometimes given during the third trimester of pregnancy to reduce transmission to offspring. Pups should be treated at 2 weeks, then every 2 weeks until weaned.

In cats, the queen is given a dewormer before breeding and after littering. Kittens can begin treatment with an adulticide dewormer by 4 weeks of age.[7] Table 9-34 outlines antihelmintic therapy for hookworm infection.

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Table 9-34 ■ Treatment of Hookworm Infections in Humans and Other Animals

Species	Primary Treatment	Alternative Treatment
Humans: cutaneous larva migrans	Ivermectin 200 mg PO qd × 1-2 days	Albendazole 200 mg PO bid × 3 days[8]
Dogs		
Adults and larvae	Fenbendazole 50 mg/kg PO × 3 days	Milbemycin oxime 0.5 mg/kg PO once, repeat monthly
Adulticide	Pyrantel pamoate 15 mg/kg PO once, repeat in 14 days	Praziquantel/pyrantel/febantel PO *or* milbemycin oxime 1, repeat in 14 days
		Ivermectin 6 mcg/kg/pyrantel PO once, repeat every month
		Dichlorvos 11 mg/kg PO once, repeat in 14 days
Cats		
Adults and larvae	Milbemycin oxime 2 mg/kg PO q30 days	Praziquantel/pyrantel PO once, repeat in 14 days
Adulticide	Pyrantel pamoate 20-30 mg/kg PO, repeat in 14 days (extralabel)	Dichlorvos 11 mg/kg PO once, repeat in 14 days

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INFLUENZA

Carina Blackmore and Peter M. Rabinowitz

Influenza (ICD-9-CM 487.1)

Other names in humans: flu, seasonal flu

Other names in animals: avian flu, bird flu, fowl plague, fowl pest, swine flu, canine flu

Influenza in humans is an acute, usually self-limited febrile respiratory illness caused by influenza virus infections. Bacterial pneumonia is a common complication in persons older than 65 years. Influenza viruses have caused human epidemics and, much less commonly, pandemics (worldwide epidemics) for at least several hundred years,[1] and influenza is still one of the most important causes of morbidity and mortality in the United States.[2] Outbreaks typically occur in the winter months in temperate climates, although they may begin in late autumn and sometimes persist to late spring months. In recent seasons, two and sometimes three different influenza viruses (two type A subtypes, one type B) have co-circulated.

Influenza pandemics can occur when a new influenza virus emerges to which the overall population lacks immunity, typically to a new hemagglutinin subtype (Figure 9-62). The emergence of a pandemic influenza strain has been associated with reassortment of gene segments between human and animal strains. Characteristic traits of pandemics include concurrent, widespread outbreaks of influenza throughout the world, sometimes outside the usual influenza season, with high attack rates in all age groups.[1] Pandemics are usually associated with substantial increases in mortality.
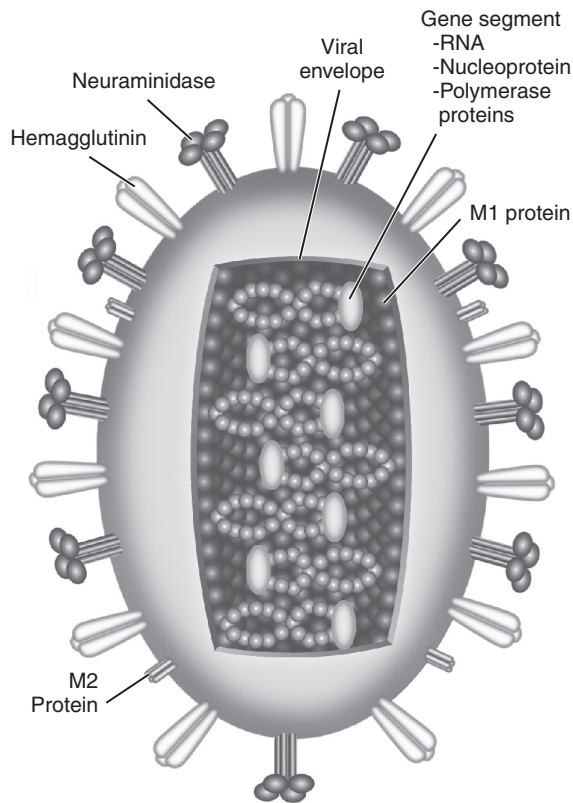
Figure 9-62 ▪ Schematic model of an influenza A virus. (From Mandell GL, Bennett JE, Dolin R (eds): *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2005, Churchill Livingstone Elsevier.)

Influenza viruses affect a number of different species, including birds, swine, horses, and dogs, but animal-to-human transmission has been documented only for birds and swine. Humans may transmit human influenza virus to pet ferrets and swine.[3] The epizootic of H5N1 high pathogenicity avian influenza in domestic and wild birds in Asia, Europe, and Africa has focused increased attention on the potential of influenza viruses to cross species barriers and cause human disease, although this is still considered a rare event and the H5N1 epizootic has not, to date, produced a pandemic virus. Dogs and cats have become naturally and experimentally infected with avian influenza viruses but have not as yet been shown to transmit the infection to humans. A swine influenza A H1N1 virus that emerged in Mexico in the spring of 2009 has further underscored the zoonotic nature of this disease. Human cases were identified worldwide within 1 week after the cause of the outbreak had been identified. As of October 25, 2009, the World Health Organization had confirmed more than 440,000 humans infected with the pandemic H1N1 virus and 5700 deaths worldwide (http://www.who.int/csr/don/2009_10_30/en/index.html). Human-to-animal transmission of the virus has also caused outbreaks in swine and turkeys (http://www.fao.org/news/story/en/item/29532/icode/).[4] H1N1 influenza infection has also been documented in ferrets and a cat (http://www.usda.gov/documents/FINAL_RESULTS_2009_PANDEMIC_H1NI_INFLUENZA_CHT.pdf).

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Educate the public and human health care providers about the importance of good cough etiquette (e.g., coughing into your elbow), handwashing practices, and seasonal influenza immunizations for their at-risk patients and for themselves.
- Encourage older individuals to get the pneumococcal (*Streptococcus pneumoniae*) vaccine.
- Educate human health care providers and veterinary clinicians about groups at risk for influenza and its complications, as well as signs and symptoms of the disease in different age groups.
- Educate travelers to countries where avian influenza is circulating about the risk of infection from contact with poultry and environments contaminated with poultry feces and secretions and uncooked poultry, and advise them to seek medical care immediately if signs (e.g., fever, cough) appear.
- Instruct health care workers with influenza-like illness not to provide direct patient care.
- Be aware of pandemic influenza (panflu) planning in your area (http://www.pandemicflu.gov/).

Human Health Clinicians

- Consider testing patients in whom influenza develops early or late in the influenza season, those with unusually severe clinical symptoms, a history of potential exposure to avian or swine influenza, or who are candidates for antiviral treatment.
- Advise symptomatic individuals to avoid caring for sick or immunocompromised individuals.
- Educate ill patients about the importance of covering their cough, keeping their distance from others, and washing their hands.
- Be aware of CDC guidance for detection and testing of avian influenza infections in returning travelers. See Travelers' Health; http://wwwn.cdc.gov/travel/content AvianFluPassengerChecks.aspx.
- Report influenza cases to state or local health department if required in state.
- Recommend influenza vaccinations to high-risk groups. The ACIP publishes annual recommendations on influenza vaccinations. At the time of publication, yearly vaccinations were recommended for the following groups[5]:
  ○ All persons who want to reduce the risk of becoming ill with influenza or of transmitting influenza to others
  ○ All children aged 6 months to 18 years
  ○ All persons aged 50 years and older
  ○ Women who will be pregnant during the influenza season
  ○ Adults who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus)

- Adults who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus
- Adults who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration
- Residents of nursing homes and other long-term care facilities
- Health care personnel (Figure 9-63)
- Healthy household contacts and caregivers of children younger than 5 years and adults 50 years and older, with particular emphasis on vaccinating contacts of children younger than 6 months
- Healthy household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

- Two vaccines, a trivalent inactivated influenza vaccine (TIV) and a live, attenuated intranasal vaccine (LAIV) are approved by the Food and Drug Administration (FDA). The TIV is approved for use in people 6 months of age or older. The primary series for children younger than 9 years consists of 2 doses administered 1 month apart. Individuals who only received 1 dose in their first year of vaccination should receive 2 doses in the following year. The TIV is injected into the deltoid muscle of older children and adults. Infants and young children without adequate deltoid muscle mass should be vaccinated in the anterolateral aspect of the thigh. The LAIV is made from a weakened virus and can cause mild illness in some individuals (runny nose, headache, sore throat, or cough). It is approved in healthy people (without underlying health problems predisposing them to complications from influenza) between 2 and 49 years who are not pregnant. Two doses of LAIV administered at least 4 weeks apart are recommended for 2- to 8-year-old children who are receiving an influenza vaccine for the first time. If the child receives only 1 dose in the first year, 2 doses are recommended the following year. The intranasal

Figure 9-63 ▪ Health care professional receiving an intramuscular vaccination. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

vaccine comes in a prefilled, single-use sprayer containing 0.2 mL of the product. Approximately 0.1 mL (i.e., half of the total sprayer contents) is sprayed into one of the nostrils and the second half of the vaccine dose is administered into the other nostril.
- Clinicians should strongly consider seasonal influenza vaccination for poultry and swine workers.[6]
- CDC guidance for detection, testing, and treatment of patients infected with the pandemic H1N1 virus and recommendations for vaccination of people at risk for infection with the novel virus strain can be found at: http://www.cdc.gov/H1N1FLU.
- At the time of publication, CDC guidance for detection, testing and treatment of patients infected with the pandemic H1N1 virus and recommendations for vaccination of people at risk for infection with the novel virus strain were at: http://www.cdc.gov/H1N1FLU/.
- Public health recommendations regarding influenza change rapidly. Please consult the WHO (www.who.int) and CDC (www.cdc.gov) websites for up to date information.

Veterinary Clinicians

- Contact state veterinarian and public health department to report suspected or confirmed cases of animal influenza.
- Wear appropriate PPE when examining animals with suspected influenza infection. This includes gloves and surgical masks—if a highly pathogenic avian influenza, swine influenza, or human influenza strain is suspected, an N-95 respirator should be used.
- Test and isolate sick animals.
- Use appropriate infection control measures in the practice (hospital and clinic) to avoid environmental contamination and nosocomial spread of the virus.[7]
- Educate the animal owner regarding zoonotic risk (where applicable) and need for adequate PPE and handwashing. Offer direct communication with family physician.
- Counsel ferret owners that these pets are susceptible to several human influenza strains.
- Be aware of the USDA's National Highly Pathogenic Avian Influenza (HPAI) Response Plan. Should HPAI be identified in the United States, a team of federal and state officials will be deployed to the area to assess the scope of disease and the resources needed to confine it.
- Veterinarians and veterinary staff should receive annual seasonal influenza vaccinations.
- If an outbreak of HPAI is identified in wild birds, consider diagnosis in domestic birds or bird predators with clinical signs and potential virus exposure.
- Influenza virus vaccines are available for swine, dogs, horses, and domestic birds. Several inactivated whole-virus swine influenza vaccines are currently on the market. The vaccines help reduce the severity of disease in pigs but do not provide complete protection against infection. Many in the swine industry use autogenous vaccines produced against the strain circulating in their herd. Animals are usually vaccinated during the late nursing–early weaning stage to prevent

influenza outbreaks in the growth/early finishing animals. Breeding herds are often vaccinated as well.

- All horses in contact with other equines should be vaccinated against equine influenza. Three types of equine influenza virus vaccines are available.[8] Inactivated vaccines and canary pox vector vaccines are administered intramuscularly. The initial series consists of 2 doses of vaccines given 3 to 6 weeks apart followed by boosters every 6 months. Annual influenza vaccine boosters may be sufficient for horses at low risk of exposure once they have been primed with 3 doses of vaccine over a 7-month period. The third vaccine type, modified live cold-adapted vaccines, is administered intranasally. One priming dose is recommended followed by boosters every 6 months. The intranasal vaccines are licensed for nonpregnant horses older than 11 months. Inactivated vaccines are licensed for horses older than 6 months, and canary pox virus vaccines are safe for foals 4 months of age or older.

- Vaccination of poultry against avian influenza is not routine because most poultry in developed countries, including the United States, are grown in commercial settings that are free from avian influenza. Vaccines have been used in specific high-risk situations targeting a known hemagglutinin subtype of avian influenza virus, such as in outdoor-reared turkeys in the upper Midwest United States when in contact with avian influenza–infected migratory ducks, or for turkeys in areas of high swine concentration. Avian influenza vaccination requires approval of the state veterinarian, and with H5 and H7 avian influenza, the approval of the USDA. Most licensed vaccines are inactivated whole avian influenza virus in oil-emulsified adjuvant, which requires individual bird handling and subcutaneous or intramuscular injection. One fowl poxvirus recombinant containing an influenza H5 hemagglutinin gene insert is licensed for emergency use. The vaccines protect against clinical disease but HPAI viruses can circulate undetected in a vaccinated flock. Serological tests cannot distinguish between an antibody response to the vaccine and a natural infection.[3]

Agent

Influenza viruses (Family Orthomyxoviridae) are enveloped, segmented, negative-stranded RNA viruses covered with two surface glycoproteins (Figure 9-64).[1] They are divided
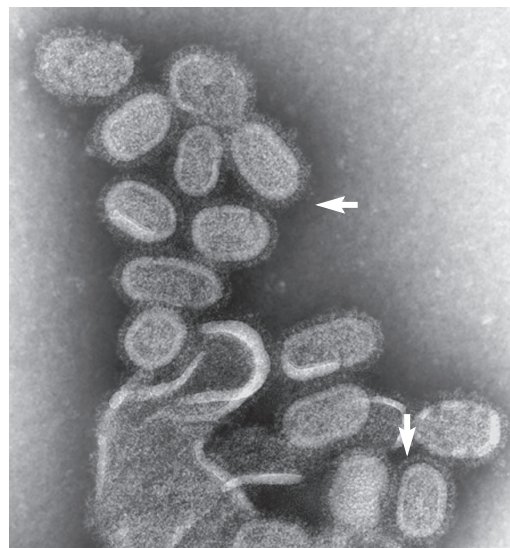

Figure 9-64 ■ Electron micrograph of influenza viruses. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

into three distinct types (A, B, and C) on the basis of their M and nucleocapsid proteins.[9] Influenza A viruses are further divided into subtypes based on the antigenic characteristics of their hemagglutinin (H) and neuraminidase (N) surface glycoproteins. Each virus carries one H and one N glycoprotein type (see Figure 9-63). Sixteen hemagglutinin subtypes (H1 through H16) and 9 neuraminidase (N1 through N9) have been identified from avian hosts.[10] Seasonal human influenza A viruses recognized to date have possessed H1, H2, or H3 and N1 or N2 glycoproteins. Influenza A (H1N1) and A (H3N2) have been circulating worldwide in human populations since 1977. Influenza B, which occurs only in humans and seals, is also responsible for significant human morbidity globally each year.[5] Influenza C is rarely recognized in comparison to A and B viruses but can cause focal human epidemics.

New seasonal influenza viruses evolve from point mutations (antigenic drift) in the surface glycoproteins, particularly the H, which frequently happens during viral replication. Gene segment reassortment among influenza A viruses can also occur. If these reassortments involve human and animal influenza viruses, they may lead to significant antigenic changes (antigenic shifts) that can result in the emergence of a novel virus subtype (Figure 9-65).
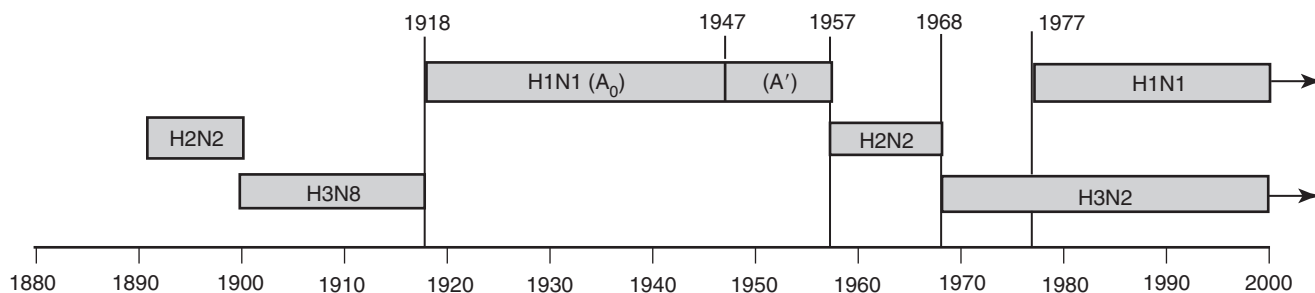

Figure 9-65 ■ Recent pandemics of influenza. The duration of circulation of viruses of various subtypes is shown by the boxes. The nature of influenza epidemics before 1918 is known only by serological means. (From Mandell GL, Bennett JE, Dolin R (eds): *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2005, Churchill Livingstone Elsevier.)

Influenza viruses exhibit various degrees of host adaptation with easy transmission between individuals within the same species, and greater difficulty of infection and unsustainable transmission to unrelated host species.[11,12] The basis of this host or species adaptation is unclear, but the presence of the proper constellation of gene segments is critical and may include specific hemagglutinin binding to receptors on host cells, especially respiratory cells, and their differential distribution; cleavability of hemagglutinin protein; presence or absence of glycosylation sites on the hemagglutinin; length of neuraminidase protein and its affinity for the sialic acids; and ability of polymerase complex to function within the host cell.[13]

Strains of avian influenza virus are classified as low pathogenic (LP) or high pathogenic (HP) based on their lethality in chickens.[14] Currently HPAI H5N1 is circulating in Asia, Europe, and Africa. However, other highly pathogenic strains have caused outbreaks in the recent past, including H7N7, H7N3, and H5N2. All HPAI viruses have been H5 and H7, but most H5 and H7 viruses are of low pathogenicity.

Geographical Occurrence

Worldwide.

Groups at Risk

Several population groups are at high risk for complications of seasonal influenza, including people who are 50 years old or older and people with chronic health problems, such as cardiovascular disease, renal and metabolic disorders (including diabetes), and respiratory disorders (including asthma). Other high-risk groups include women who are pregnant during the flu season, children and adolescents who are receiving long-term aspirin therapy, and children younger than 5 years.[15] Severe influenza disease is also often seen in individuals with immunosuppressive disorders such as cancer or HIV/AIDS.[5]

Individuals performing activities involving close contact with animals, such as slaughtering animals and defeathering birds, have been reported to be at increased risk for avian and swine influenza.[16-18]

Hosts, Reservoir Species, Vectors

Avian influenza viruses are maintained in nature by wild birds. The viruses have been isolated from more than 100 bird species in 13 genera; however, the most important avian influenza reservoir hosts belong to the Anseriformes (ducks, geese, and swans) and the Charadriiformes (gulls, terns, and shorebirds) groups.[19] More virus isolations have been reported from Mallards (*Anas platyrhynchos*) than any other bird species. Certain influenza virus strains have adapted to genetically distinct horse, swine, poultry, dog, and human viruses and are self-sustaining in those species.[19-21] Incidental hosts or sporadic infections have been reported in mink, ferrets (Figure 9-66), stone marten, domestic cats, large felids (tigers and leopards), and sea mammals.[19,22]

Swine are susceptible to both human and avian virus strains and are hypothesized to be able to serve as viral mixing vessels where human and avian gene segments may reassort.[1] The 2009 H1N1 swine influenza virus is a novel reassortant of two
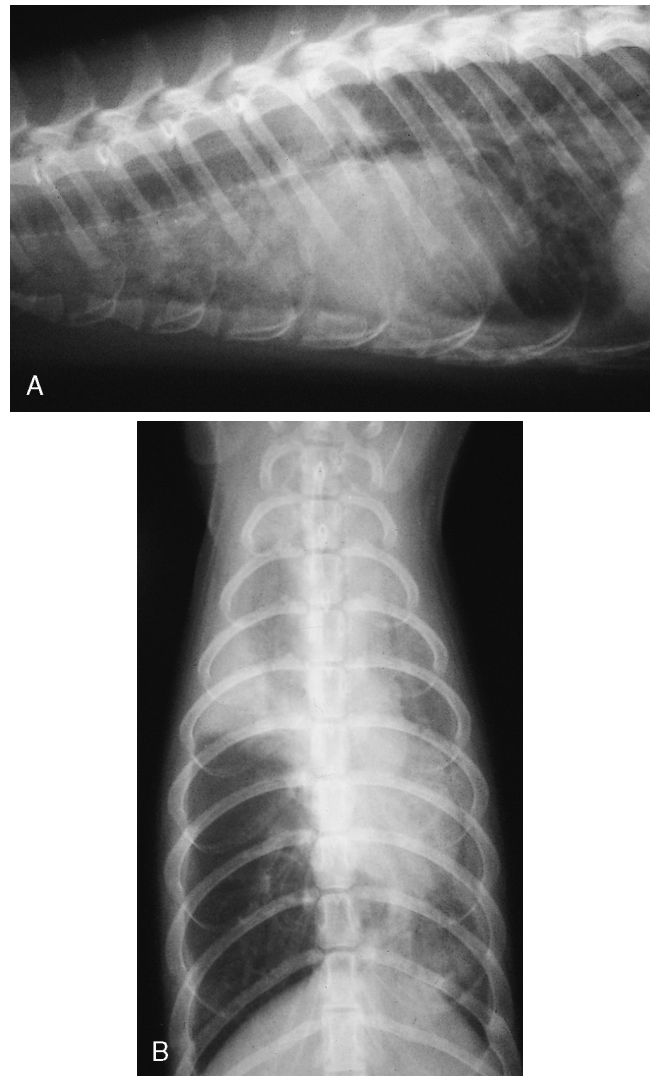

Figure 9-66 ▪ Lateral (**A**) and ventrodorsal (**B**) radiographs of a ferret with bacterial pneumonia as a complication of influenza. (From Quesenberry K, Carpenter JW: *Ferrets, rabbits and rodents: clinical medicine and surgery*, ed 2, St Louis, 2004, Saunders Elsevier.)

(parent) swine influenza viruses. It also contains genes of avian and human influenza virus origin incorporated into one of the parent viruses at an earlier time.[23] However, reassortment in swine may not be a requirement for emergence of a pandemic strain if the avian strain can produce infection in a human host.

Mode of Transmission and Life Cycle

Human influenza is usually spread from person to person in close contact through large-particle respiratory droplet and short-distance small-particle aerosol transmission (coughs, sneezing) (Figure 9-67). Indirect spread via contact with surfaces contaminated with respiratory droplets is also a possible transmission mode, and there is evidence that the virus can persist for 1 to 2 days on some surfaces.[5]

In swine, the virus is found in respiratory secretions and spreads by aerosolization and by direct pig-to-pig contact.[24] Birds can shed high concentrations of influenza virus in feces, and fecal/oral spread is believed to be an important route of
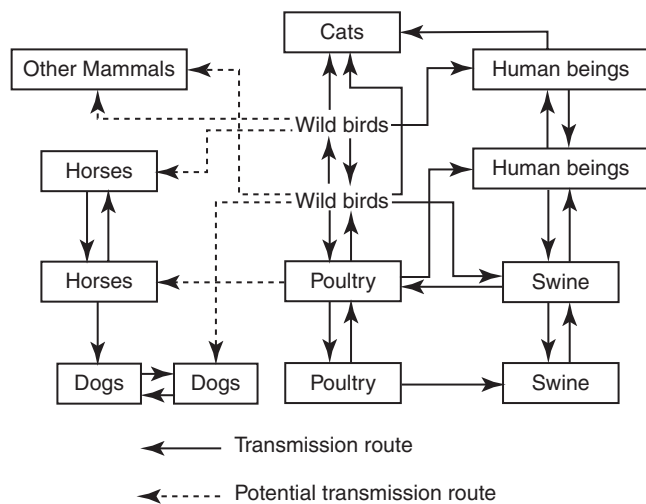
Figure 9-67 ■ Life cycle of influenza.

virus transmission in wild birds.[19] Infected birds can also shed influenza virus in their saliva and nasal secretions. Poultry can become infected when they have direct contact with infected birds or indirectly through contact with contaminated surfaces (such as equipment or cages) or feed or water. Aerosol transmission may also be possible over short distances.[25]

Touching surfaces contaminated with avian influenza virus in respiratory droplets and handling infected birds or bird manure are hypothesized risk factors for human infection with avian influenza, possibly through contaminated-hand–to–mucous membrane contact or inhalation of contaminated dust particles or aerosols generated during cleaning, slaughtering, defeathering, and other activities.[16,18] Swine influenza transmission appears to occur during close direct or indirect human contact with infected swine.[17]

Environmental Risk Factors

As stated previously, it is believed that contaminated environments such as surfaces, aerosols, and water may play a role in animal-to-animal influenza transmission and may also be important in human-to-human and animal-to-human transmission, although the significance of such environmental spread in each circumstance is not well understood.

Human crowding, such as in nursing homes, is associated with an increased rate of human outbreaks. As in animals, a high density of birds or swine in a production facility or a live animal market, as well as mixing of waterfowl, poultry, and other animal species including swine in a single facility, may facilitate the spread of virus between animals. Farms that have ponds or other water bodies where wild waterfowl can come in contact with domestic animals may also constitute an environmental risk. Whether the seasonal pattern of influenza is related to other environmental variables such as temperature and humidity remains unclear.

Disease in Humans

Influenza virus infections can affect all age groups, although the highest infection rates are seen among infants and children. Upper and lower respiratory tract complications occur across age groups, but hospitalizations and deaths from infection are more common in people older than 65 years.

Uncomplicated influenza typically has a quick onset of fever, myalgia, headache, malaise, sore throat, and nonproductive cough. Rhinitis may also be present. Otitis media, nausea, and vomiting are other common influenza manifestations among children. Young children may be less likely than other influenza cases to present with fever and cough.[5] The incubation period is short (1 to 4 days) and the morbidity period generally lasts 3 to 7 days. Lassitude and cough may persist for 2 weeks or more.[26] Adults may be infectious the day before through day 5 after disease onset. Young children may shed virus several days before and after symptom onset.[5]

Complications of influenza are common. Patients may develop primary viral pneumonia, viral or secondary bacterial sinusitis and otitis, or pneumonia and experience exacerbations of underlying medical conditions such as pulmonary or cardiac disease. Influenza virus infection also has been uncommonly associated with encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome.[5]

Humans can on rare occasions become infected with avian[27] or swine[19,28] influenza viruses. Symptoms range from a mild conjunctivitis or upper respiratory tract disease to pneumonia, acute respiratory distress, and death. Further human-to-human transmission of these animal influenza viruses has been reported but is uncommon.

Disease in Animals

Avian influenza (AI) viruses are classified into low pathogenicity (LP) and high pathogenicity (HP) based on specific criteria related to their ability to produce high mortality rate in chickens or have a hemagglutinin protein cleavage site sequence compatible with previous HPAI virus.[29] Most AI strains are LP and generally cause no or few clinical signs in poultry. Typical clinical signs associated with LPAI reflect an upper respiratory tract disease or reproductive disease in hens (i.e., drops in egg production with abnormal eggs). However, some H5 and H7 LPAI viruses have mutated into HPAI viruses in the field. Signs of HPAI include high mortality rate; sudden death without premonitory clinical signs; lethargy; severe decrease in egg production; facial edema with swollen eyelids, comb, wattles, and hocks; purple discoloration of the wattles, combs, and legs; upper respiratory tract signs; incoordination; and diarrhea.[30] Turkeys are susceptible to certain strains of H1 and H3 swine influenza viruses.[31,32]

Swine influenza A H1N1 and H3N2 viruses are endemic in swine populations in the United States.[33] Clinical signs of influenza in pigs include fever, coughing, nasal and/or ocular discharge, dyspnea, and depression. Reproductive problems are seen in both males and females. Milk production may also be reduced. The morbidity period is usually 5 to 7 days. Morbidity can reach 100%. Mortality rates are low, usually between 1% and 3%; however, secondary bacterial infections may develop and increase mortality.[25]

Influenza A viruses H3N8 and H7N7 cause equine influenza in horses and other equids. The incubation period is generally 1 to 3 days. Incubation periods as long as 7 days have been reported. Clinical signs include fever; a harsh, dry cough; and serous to mucopurulent nasal discharge. In partially immune or vaccinated animals, one or more of these signs may be absent. Other typical signs include depression, muscle

soreness, anorexia, and enlarged submandibular lymph nodes. Young foals lacking maternal antibody protection are susceptible to a fatal viral pneumonia. Horses can also develop a potentially fatal secondary bacterial pneumonia, pleuropneumonia, and myocarditis.[8,34]

Infected horses may shed virus over an extended period starting during the incubation period and ending a week or more after apparent recovery. Peak viral shedding is thought to occur during the first 24 to 48 hours when the animal is febrile.[8] The virus is spread via aerosolized respiratory droplets and fomites with an attack rate that can approach 100% in susceptible populations.

Canine influenza was first recognized in 2004. An equine influenza virus A H3N8 strain has apparently adapted to dogs and causes outbreaks of respiratory disease. Most animals develop a mild cough, purulent nasal discharge, and low-grade fever.[21] Dogs can also develop a more severe disease with high fever and pneumonia. Between 5% and 10% of ill dogs die from the illness.[21,35]

Avian influenza can cause fatal infection in domestic and large cats. Reported signs of HPAI H5N1 in felids include fever, panting, nervousness, and depression.[36] Table 9-35 shows comparative clinical presentations in humans and other animals.

Table 9-35 ■ Influenza: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans	Close contact with infected person, bird, or swine	1-4 days	Fever, myalgia, headache, malaise, sore throat, nonproductive cough and rhinitis, otitis media, and gastrointestinal symptoms in children; complications include primary viral pneumonia, secondary bacterial sinusitis, otitis, or pneumonia, exacerbated underlying medical conditions such as pulmonary or cardiac disease	DFA, RT-PCR, EIA, viral cultures, and rapid diagnostic tests such as immunochromatographic assays, paired sera taken 2-4 weeks apart
Birds	Direct contact with secretions or feces from infected birds, contaminated feed, water, equipment, or clothing	1-5 days	LPAI: No or few clinical signs, including inappetence, mild respiratory signs (nasal discharge, coughing, sneezing), and decreased egg production	RRT-PCR and serological screening tests, virus isolation, sequencing, and chicken pathogenicity test needed for confirmation of HPAI; serology by ELISA and AGID are used for monitoring
	Movement of people and birds		HPAI: Sudden death; lethargy; decreased egg production, soft-shelled or misshapen eggs; facial edema with swollen eyelids, comb, wattles, and hocks; purple discoloration of the wattles, combs, and legs; incoordination; and diarrhea	Histopathology findings with HPAI include hemorrhaging and necrosis of multiple organs[19]
Swine	Contact with nasal secretions or aerosol; airborne spread of virus can occur between farms under certain circumstances	<24 hours	Fever; coughing; nasal and/or ocular discharge; dyspnea and depression Reproductive problems such as reduced viability of sperm, first- and second- trimester abortions, delayed return to estrus, and decreased viability of piglets; milk production may also be reduced	Lung or nasal tissues can be evaluated for the presence of live or inactivated virus using immunohistochemistry, DFAs, antigen-capture ELISA, cell culture, or PCR Tests for detecting H1N1 or H3N2 antibodies include the HI, ELISA, immunodiffusion, and IFA
Horses	Aerosolized respiratory secretions; contaminated equipment, brushes, or rugs	1-3 days	Clinical signs include fever; a harsh, dry cough; and serous to mucopurulent nasal discharge; other typical signs include depression, muscle soreness, anorexia, enlarged regional lymph notes, colic, edema of the extremities and scrotum, viral pneumonia in young foals; secondary bacterial pneumonia, pleuritis, and interstitial myocarditis	Viral antigen can be detected from nasopharyngeal swabs, and tracheal and nasal wash samples using virus isolation, RT-PCR, nested RT-PCR, and ELISA Paired acute and convalescent serum samples can be submitted for HI testing
Dogs	Contact with aerosolized respiratory secretions and contaminated objects	2-5 days	Moist or dry cough, purulent nasal discharge, fever, pneumonia	Paired sera taken 2-3 weeks apart, virus detection from nasal swabs by PCR or viral culture[37]
Cats	Predation on diseased birds	2-5 days	Fever, dyspnea, depression, conjunctivitis	Paired sera, pharyngeal swabs[36]

AGID, Agar gel immunodiffusion; *DFA*, direct immunofluorescent antibody; *ELISA*, enzyme-linked immunosorbent assay; *HI*, hemagglutination-inhibition; *IFA*, immunofluorescent antibody; *RT-PCR*, reverse transcriptase polymerase chain reaction; *EIA*, enzyme immunoassay; *RRT-PCR*, real-time reverse transcriptase polymerase chain reaction.

Diagnosis

Diagnosis in Humans

The differential diagnosis for human influenza includes other respiratory pathogens, including *Mycoplasma pneumoniae,* adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza viruses, and *Legionella* species infection.[26] Studies have estimated that 80% to 90% of healthy adults presenting with an acute onset of fever and a cough, the most common presentation of influenza, in areas with confirmed influenza activity have the disease. Young children and older adults are less likely to present with these symptoms. Infants may present with high fevers. A septicemia-like disease, cough, and fever are seen in 64% of children younger than 5 years, and fewer than one in three nonhospitalized patients 60 years or older present with typical influenza signs.[5]

Laboratory confirmation of disease is important. Specimens should be collected the first few days after onset of symptoms or no more than a week after disease onset in young children. The most common diagnostic tests currently used in clinics, doctors' offices, and hospitals are rapid influenza tests using immunochromatography. These tests require no reagent additions or wash steps, usually detect both influenza A and B, and use respiratory tract specimens specified in the manufacturers' instructions.[38] Results are available within 30 minutes. The accuracy of these tests depends on the sensitivity and specificity of the assay, the amount of virus in the sample, and the specimen type used. Infants and young children shed the highest viral titers, and these tests perform best in this patient group. The rapid tests typically have greater than 90% specificity and an average 70% sensitivity for detecting influenza. False-positive results are more common when the prevalence of influenza is low; false-negative results are more likely to occur when disease prevalence is high.

Additional diagnostic tests available in hospital and other clinical laboratories include viral cultures, direct immunofluorescence antibody (DFA) on clinical specimens, reverse transcriptase polymerase chain reaction (RT-PCR), and enzyme immunoassay (EIA). The ideal specimen depends on the test used but may include nasopharyngeal and nasal swabs or aspirates, nasal and bronchial washes, throat swabs, or sputum collected within the first 4 days of illness. Results from antigen tests such as DFA or EIA should be available within a few hours of arrival at the laboratory. Conventional viral cultures can take between 2 and 10 days, whereas rapid centrifugation cultures followed by IFA staining are reported at 1 and 2 days. RT-PCR assays are currently confined to reference laboratories and some large tertiary care hospitals, and where available are performed no more than once a day. Influenza virus infection can be confirmed by serology as well. Paired acute and convalescent sera taken 2 to 4 weeks apart are needed.[5]

Serological and rapid tests for human influenza A may not recognize avian influenza viruses (such as influenza A H5N1).

Diagnosis in Animals

Animal influenza is diagnosed based on clinical signs and laboratory test results. Antigen can be recovered from respiratory secretions in horses, swine, and dogs the first few days after disease onset. Optimal specimens include nasal secretions and lung tissue from swine, nasopharyngeal swabs from horses, nasal swabs from dogs, and oropharyngeal swabs from birds. Serological testing is another valuable diagnostic tool in animals. Acute and convalescent samples taken 2 weeks apart are needed.

In poultry, samples of oropharyngeal and cloacal swabs are preferred for diagnosis. In the United States, matrix gene real-time reverse transcriptase polymerase chain reaction (RRT-PCR) is used to identify influenza A virus and all positives are further tested by H5 and H7 specific RRT-PCR. The hemagglutinin proteolytic cleavage site is sequenced for all H5 or H7 RRT-PCR+ samples to determine LP or HP. The avian influenza virus detection is confirmed by virus isolation in 9- to 11-day embryonating chicken eggs. All influenza A viruses are subtyped by hemagglutination-inhibition (HI) and neuraminidase-inhibition (NI) tests and pathotyped by in vivo chicken pathogenicity testing. Serological monitoring of poultry is done using commercial ELISA and agar gel immunodiffusion (AGID) tests for influenza A, and positives are subtyped by HI and NI tests.

Treatment

Treatment in Humans

Four antiviral medications—amantadine, rimantadine, oseltamivir (Tamiflu), and zanamivir (Relenza)—are approved by FDA for influenza treatment.[39] The first two are not currently recommended because of the widespread presence of antiviral resistance in influenza A (H3N2) viruses and lack of activity against influenza B. The latter two drugs are neuraminidase inhibitors with activity against both influenza A and B viruses. Early treatment reduces illness severity and risk of complications leading to antibiotic use. In hospitalized adults, oseltamivir treatment appears to reduce the likelihood of influenza-related mortality. Antiviral resistance also occurs to the neuraminidase inhibitors, and during the 2007-08 Northern Hemisphere season, community circulation of oseltamivir-resistant H1N1 viruses was noted for the first time.

Treatment should be started as soon as possible after disease onset. Oseltamivir is approved for treatment of people 1 year of age and older. Zanamivir is approved for treatment of people 7 years of age and older. Both drugs can also be used as chemoprophylaxis with a disease prevention efficacy ranging from 70% to 90%. Zanamivir is not recommended for persons with underlying airways disease (e.g., asthma or chronic obstructive pulmonary disease). Table 9-36 outlines treatment guidelines for symptomatic disease in humans.

Treatment in Animals

Treatment of influenza in horses, dogs, and pigs is generally supportive. Antivirals as listed above for humans are not approved for treatment of animal infections, in part due to concern about development of drug resistance.

Table 9-36 ▪ Treatment Guidelines for Symptomatic Influenza Disease in Humans

Antiviral Agent		Age Group (yr)				
		1-6	7-9	10-12	13-64	≥65
Zanamivir*	Treatment, influenza A and B	N/A†	10 mg (2 inhalations) twice daily			
	Chemoprophylaxis, influenza A and B	Ages 1-4 N/A	Ages 5-9 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily		
Oseltamivir	Treatment,‡ influenza A and B	Dose varies by child's weight§			75 mg twice daily	
	Chemoprophylaxis, influenza A and B	Dose varies by child's weight‖			75 mg/day	

NOTE: Zanamivir is manufactured by GlaxoSmithKline (Relenza—inhaled powder). Zanamivir is approved for treatment of persons 7 years and older and approved for chemoprophylaxis of persons 5 years and older. Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu—tablet). Oseltamivir is approved for treatment or chemoprophylaxis of persons 1 year and older. No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children younger than 1 year. This information is based on data published by the CDC (http://www.cdc.gov/h1n1flu/recommendations.htm).
*Zanamivir is administrated through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease.
†Not applicable.
‡A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance less than 30 mL/min.
§The treatment dosing recommendation for children weighing 15 kg or less is 30 mg twice a day; for children weighing more than 15 kg and up to 23 kg, the dose is 45 mg twice a day; for children weighing >15-23 kg, the dose is 45 mg twice a day; for children weighing >23-40 kg, the dose is 60 mg twice a day; and for children >40 kg, the dose is 75 mg twice a day.
‖The chemoprophylaxis dosing recommendation for children weighing 15 kg or less is 30 mg once a day; for children weighing >15-23 kg, the dose is 45 mg once a day; for children weighing >23-40 kg, the dose is 60 mg once a day; and for children >40 kg, the dose is 75 mg once a day. From http://www.cdc.gov/flu/professionals/antivirals/dosage.htm#table.

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LEISHMANIASIS

Peter M. Rabinowitz and Lisa A. Conti

Cutaneous leishmaniasis (ICD-10 B55.1, B55.2)

Other names in humans: Aleppo ulcer, Baghdad or Delhi boil, Oriental sore, Espundia, uta, chiclero ulcer

Visceral leishmaniasis (ICD-10 B55.0)

Other names in humans: kala-azar

Other names in animals: canine visceral leishmaniasis

Leishmaniasis caused by infection with protozoans in the genus *Leishmania* causes millions of infections each year around the world. The infection takes two basic forms: cutaneous and visceral, but disease syndromes may overlap. The severity of human infection ranges from mild skin lesions to severe disfiguring facial involvement or systemic disease with organ failure and death. This zoonotic disease is transmitted by insect vectors, usually of the phlebotomine sand fly family. Leishmaniasis has been transmitted directly from dog to dog in the United States. Worldwide risk of leishmaniasis is increasing in both humans and animals. Factors responsible may include the transboundary movement of humans and animals, global climate change affecting the distribution of vectors, the HIV epidemic,[1] and increasing contact of humans with wilderness areas where the disease is endemic. In addition to being a disease of travelers returning to the United States, there is an expanding focus of human cases of leishmaniasis in Texas, as well as an ongoing outbreak of canine visceral leishmaniasis in foxhounds in the eastern United States. The complex interrelationships of leishmaniasis infection in animals and humans demand ongoing cooperation between animal and human health professionals to detect new cases and better control this challenging disease.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Characterize the risk in the community, including whether the sand fly vector is present and if there is evidence of transmission to humans or domestic animals.
- Educate human health providers that infection could be spread through shared needles.

- Conduct an immediate investigation of a human or veterinary case to determine whether it is related to travel or local transmission.
- In endemic areas, develop a strategy with vector specialists for vector control based on local ecology and transmission patterns. Interventions may include targeted spraying in suspected sand fly habitat, including around doorways of dwellings (if residential transmission suspected), stone walls, animal houses, and garbage dumps.
- In endemic areas where dogs are serving as a reservoir, work with animal control authorities on effective strategies including use of insecticide-impregnated collars. Culling of dog populations has not been proven effective in some areas.[2]
- Ensure that travelers to endemic areas take steps to avoid sand fly bites. Use insect repellent and permethrin-impregnated bed nets and protective clothing.[2]

Human Health Clinicians

- Consider the diagnosis in all patients with a history of recent travel or residence in an endemic area.
- Immediately report disease to public health authorities.
- Counsel travelers to endemic areas about risk reduction in terms of avoiding sand fly bites (see above).

Veterinary Clinicians

- Consider the diagnosis in dogs in the United States, especially foxhounds, who present with constitutional signs.
- Consider the diagnosis in equids with nonhealing cutaneous lesions on the head.
- Counsel clients not to let cats and dogs roam outside and to provide insect repellent for horses in endemic areas.
- Increase index of suspicion of leishmaniasis in animals with a travel history to the Mideast, tropics, or subtropics or with previous blood transfusion.
- Be aware that autochthonous transmission of visceral canine leishmaniasis has occurred in the United States in the absence of insect vectors.[3]
- Vaccine trial work shows promise for use in endemic areas.[4]
- Treat infected dogs using the CDC protocol through the state public health veterinarian. Canine leishmaniasis may be reportable to your state health or agriculture department.

Agent

At least 20 species in the genus *Leishmania* are pathogenic in humans, and are found in a range of mammalian reservoirs and vectors. *Leishmania* are obligate intracellular protozoan parasites, with virulence and types of disease varying between the strains.[5] Visceral leishmaniasis is caused by *L. donovani, L. infantum,* and *L. chagasi*. In the United States, *L. mexicana* is the cause of cutaneous leishmaniasis in Texas. In Latin America, *L. braziliensis* causes a more aggressive form of cutaneous leishmaniasis.[6]

Geographical Occurrence

Leishmaniasis occurs in 88 countries, mainly in the tropics and subtropics, with varying patterns of disease and ecological relationships (the disease has not been reported in Australia and Oceania). In the United States, most cases are seen in travelers and their pets returning from endemic regions. There is a small focus of cases of cutaneous leishmaniasis in Texas that appears to be extending northward.[6]

Cutaneous leishmaniasis due to *L. braziliensis* and *L. mexicana* complexes occurs in Latin American countries with the exception of Chile and Uruguay. In the Eastern Hemisphere, cutaneous leishmaniasis is caused by *L. tropica, L. major,* and *L. aethiopica*; hotspots include the Indian subcontinent, China, southwestern Asia including Afghanistan and Iran, the Mediterranean region, and sub-Saharan Africa including Sudan.

In the New World, visceral leishmaniasis in humans is due to infection with *L. infantum* and *L. chagasi* and is found across Central and South America. In the Old World, *L. donovani* is the principal cause of visceral leishmaniasis, which occurs in mostly rural areas of India, Bangladesh, China, Nepal, Pakistan, southern regions of the former Soviet Union, the Middle East and Mediterranean, and sub-Saharan and East Africa.[2]

In the United States, *L. infantum* seroprevalence studies of dog kennels have identified positive results in 21 states.

Groups at Risk

Groups at increased risk for leishmaniasis include individuals who encounter the sand fly vector, including forest workers and rural residents. In areas where visceral leishmaniasis is endemic and the sand fly vector is found, dog ownership can be a risk factor for infection.[7]

Hosts, Reservoir Species, Vectors

The vectors and reservoir hosts of leishmaniasis are diverse and vary in part by geographical region and agent. Phlebotomine sand flies are most active dusk through dawn and difficult to see as they are about one third of the size of a mosquito.

In the Americas, New World cutaneous leishmaniasis has zoonotic transmission through bites of a number of sand fly species; mammalian hosts include small rodents and larger mammals. In Texas, the burrowing wood rat (*Neotoma micropus)* is the apparent reservoir for cutaneous leishmaniasis. Zoonotic Old World cutaneous leishmaniasis caused by *L. major* is spread by bites of the sand fly *Phlebotomus papatasis*.[5] A major reservoir is gerbils (*Meriones unguiculatus*). Hyraxes (*Procavia capensis)* are another mammalian host. Although dogs can be infected, they do not always serve as a competent reservoir for cutaneous leishmaniasis. A human-to-human transmission cycle of cutaneous leishmaniasis in the Old World due to *L. tropica* is spread by *P. sergenti*.

Lutzomyia species sand flies spread visceral leishmaniasis in the New World, whereas *L. donovani* is spread person to person in the Indian subcontinent and Eastern Africa by a number of sand fly species. Dogs and wild canids (foxes and jackals) are the principal animal reservoir for visceral leishmaniasis.[5]

Mode of Transmission and Life Cycle

Transmission is largely vector-borne through bites of the female phlebotomine sand fly injecting the infective, flagellated promastigote forms into the skin of a vertebrate host (Figure 9-68). The parasite then transforms into the non-flagellated amastigote (Color Plate 9-35) and multiplies within macrophages throughout the host's reticuloendothelial system. The vector cycle is complete with sand fly infection from the vertebrate host, where the organisms multiply extracellularly in the sand fly gut over 8 to 20 days to produce infectious promastigotes (see Figure 9-68).[5]

Once infected, a mammalian host appears to retain the ability to be infectious to others even after treatment. The agent may remain dormant in the host animal for years, and then infection can recur when immune status declines, such as in HIV infection, malnutrition, or administration of immunosuppressive drugs for organ transplants or other conditions. Chronically infected individuals, even after receiving treatment, can serve as a reservoir for further infection of sand fly vectors. In addition to vector-borne transmission, person-to-person transmission has been reported through blood transfusions and the sharing of needles between IV drug users.

In an outbreak of canine visceral leishmaniasis among U.S. foxhounds, transmission occurred dog to dog (but not dog to person) through direct contact with blood and secretions and transplacentally from an infected bitch to her pups. There is no evidence of vector transmission to dogs in the United States, and sand flies are not found in many of the regions where dogs are infected.[8] However, in areas where both visceral leishmaniais in dogs and sand flies occur, there is a potential risk of future episodes of vector-borne transmission from dogs to humans.

Environmental Risk Factors

Key environmental factors include the population of reservoir hosts and the population of vectors. Sand fly populations may increase with availability of breeding sites and humid areas around ponds or in tree holes. Factors that increase contact between humans and vectors and reservoirs have been tied to outbreaks, including deforestation and encroachment of human habitation into forested areas. Climate change appears to be playing a role in the extension of the ranges of some vectors and animal reservoirs.
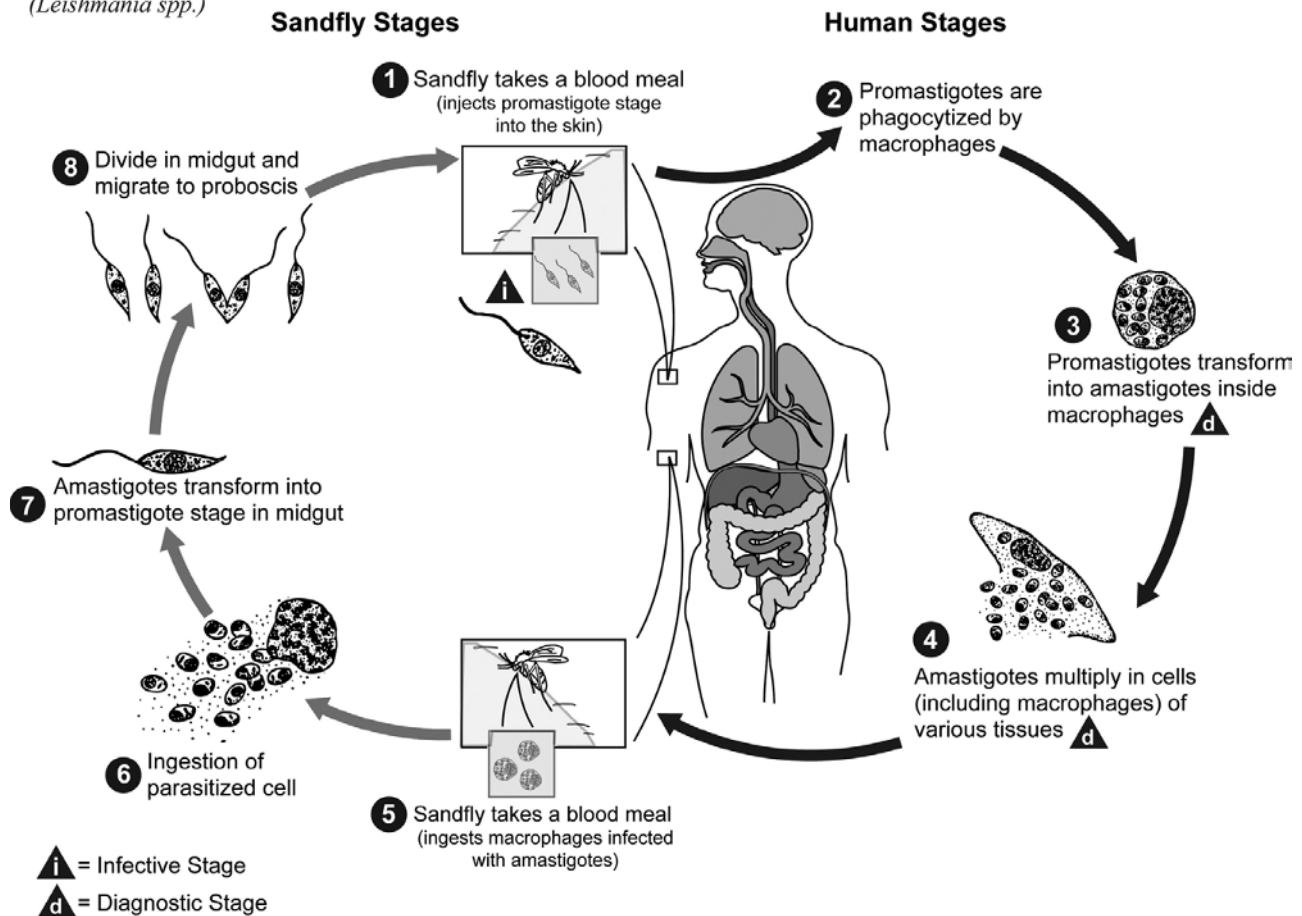
Leishmaniasis
(Leishmania spp.)

Figure 9-68 ■ Life cycle of *Leishmania* species, the causal agents of leishmaniasis. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Alexander J. da Silva and Melanie Moser.)

Disease in Humans

Table 9-37 provides clinical presentations of leishmaniasis.

Cutaneous Leishmaniasis

Each year cutaneous leishmaniasis occurs in approximately 1.5 million people worldwide. Cutaneous involvement of leishmaniasis infection can take a number of forms, depending on the species involved and the immune status of the host.

Simple *cutaneous* leishmaniasis often begins with a small macule at the site of the fly bite that progresses to a papule. The papule enlarges over time and may ulcerate.[9] In many cases, the lesions resolve spontaneously over a period of months or years (Color Plate 9-36).

Diffuse cutaneous leishmaniasis tends not to ulcerate but instead spreads gradually through the skin, causing chronic nodular lesions especially on the face and extremities. It may be a lifelong infection.

Atypical cutaneous leishmaniasis in Central America caused by *L. infantum* or *L. chagasi* is characterized by cheloid-type lesions without ulceration.[2]

Leishmaniasis recidivans caused by *L. tropica* occurs in Iran and other parts of central Asia. The tuberculoid lesions tend to involve the face, spreading outward and often relapsing. It also tends to be a chronic infection lasting for decades.[9]

Mucocutaneous leishmaniasis due to *L. braziliensis* or related species can develop in individuals years after the lesions of cutaneous leishmaniasis have healed. The symptoms may begin with nasal stuffiness but progress to respiratory and swallowing difficulties as tissue destruction involves the nose, mouth, and laryngopharyngeal regions (Color Plate 9-37).

Visceral Leishmaniasis

Visceral leishmaniasis (kala-azar), occurring in about a half million people each year, is usually due to infection with either *L. donovani* or *L. infantum.* This disease is characterized by systemic signs such as fever and weight loss. Hepatosplenomegaly, pancytopenia, and increased gamma-globulins can occur. Lymphadenopathy and abnormal liver function test results are common. In India, hyperpigmentation is part of the clinical syndrome. Although many cases resolve spontaneously, malnutrition and immunocompromised

Table 9-37 ▪ Leishmaniasis: Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans				
Simple cutaneous leishmaniasis	Exposure to sand flies, malnutrition, immunosuppression, proximity to reservoir habitat	At least a week, may be many months[2]	Macule progressing to papule with ulceration	Biopsy of lesion may demonstrate intracellular amastigotes; positive leishmanin skin test
Diffuse cutaneous leishmaniasis		At least a week, may be many months[2]	Nodular lesions spreading slowly on face and extremities	
Leishmaniasis recidivans		Develops over months to years	Relapsing lesions on face with central healing	
Mucocutaneous leishmaniasis			Tissue destruction of nose, oropharynx	
Visceral leishmaniasis		Typically 2-6 months, range 10 days to years[2]	Weight loss, fever, hepatosplenomegaly	Anemia, leukopenia, thrombocytopenia, elevated liver function tests, biopsy may show amastigotes
Dogs	Exposure to sand flies, crowding, receipt of blood products from infected donors, parturition (?)	3 months to years	May be subclinical; hyperkeratosis, chapping, weight loss, anorexia, fever, visceral involvement including renal failure	Proteinuria, elevated liver function tests Tissue biopsy and culture
Cats, Horses	Exposure to sand flies	3 months to years	Skin nodules on head	Biopsy may reveal organisms

condition predispose patients to more severe disease and the risk of fatal complications. A post–kala-azar cutaneous leishmaniasis can occur in recovered individuals. These lesions can be a reservoir for continued transmission through sand fly bites.

Disease in Animals

Dogs tend to develop systemic, visceral, and cutaneous involvement (Figures 9-69 and 9-70). Weight loss, anorexia and fever are common. Splenomegaly and lymphadenopathy occur in up to a third of affected dogs. Epistaxis, muscle atrophy, and seizures can also occur (Color Plate 9-38). The skin lesions tend to present as hyperkeratosis and chapping over the head, muzzle, and footpads. These lesions can ulcerate. Renal failure is the most common cause of death and is preceded by nausea and vomiting. Laboratory findings include hyperproteinemia, proteinuria, and elevated liver function test results.[10]

Infection in cats and horses is less common than in dogs and principally involves the skin, typically presenting with nodules on the ears (Color Plate 9-39 and Figure 9-71).[10]

Figure 9-69 ▪ Canine leishmaniasis showing exfoliative dermatitis and scaling on face. (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier.)

Figure 9-70 ▪ Dog with characteristic features of leishmaniasis. Note cachexia, muscle atrophy, and excessive scaling. (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier.)
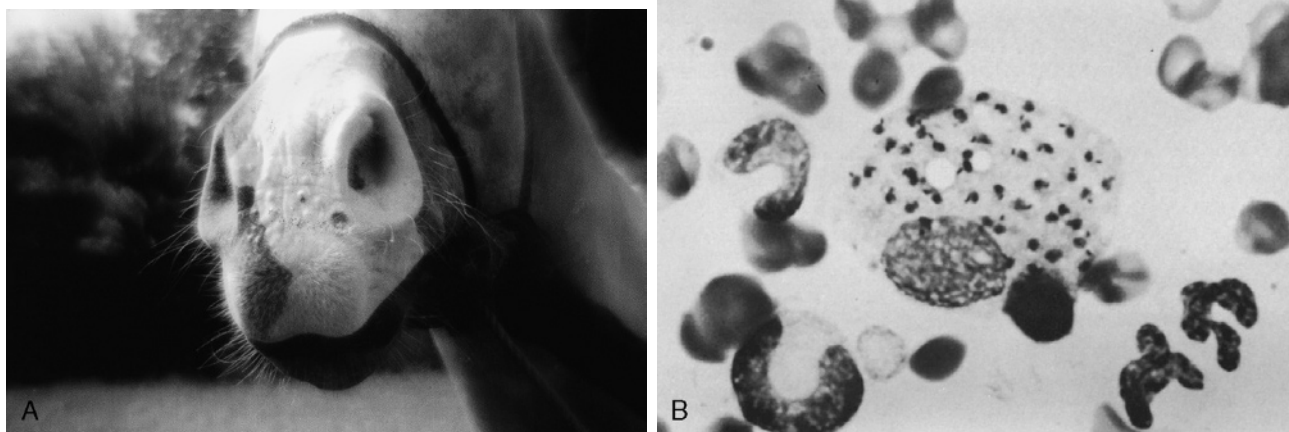
Figure 9-71 ■ Leishmaniasis. **A**, Nonhealing ulcer on muzzle. **B**, Macrophage containing numerous amastigotes (Leishman-Donovan bodies). (From Scott DW, Miller WH Jr: *Equine dermatology*, St Louis, 2003, Saunders Elsevier. *A*, Courtesy A. Sales; *B*, Courtesy T. French.)

Diagnosis

The differential diagnosis of cutaneous leishmaniasis in humans can be broad and includes sporotrichosis, cutaneous tuberculosis or atypical mycobacterial infection, blastomycosis, sarcoidosis, syphilis, and neoplasia.

The presence of suggestive lesions in the setting of a potential contact such as history of travel to an endemic area should lead one to consider the diagnosis. Definitive diagnosis is often accomplished by a biopsy of the lesion with tissue identification of amastigotes or culture of promastigotes.[9] The leishmanin skin test result is often positive in simple cutaneous leishmaniasis. PCR techniques are in development.[11]

Visceral leishmaniasis in endemic areas can be confused with other causes of fever, chronic weight loss, and splenomegaly such as malaria and schistosomiasis. The diagnosis can be made by isolating amastigotes from macrophages in a bone marrow biopsy or a splenic biopsy. The latter is considered more sensitive but involves a risk of hemorrhage.[9]

In animals, a skin biopsy can reveal the presence of intracellular organisms. Serology with IFA or ELISA is available but cross-reactions with *Trypanosoma cruzi* can occur. Biopsies of skin, spleen, bone marrow, or lymph nodes can be cultured; smears of these samples may reveal the organism.[10] A PCR test is available at some academic institutions.[12]

Table 9-38 ■ Treatment of Leishmaniasis Infection in Humans and Other Animals

Species	Primary Treatment	Alternative Treatment
Humans (Adult)		
Cutaneous: New World*	Sodium stibogluconate (Pentostam) (available through CDC) *or* meglumine antimoniate 20 mg/kg IV/IM/day in 2 divided doses × 28 days[14]	Amphotericin B 1 mg/kg IV qod × 20 doses *or* liposomal amphotericin 3 mg/kg/day × 6 days (simple cutaneous) *or* 3 weeks (mucocutaneous) *or* miltefosine 2.5 mg/kg PO qd × 28 days[14]
Cutaneous: Old World*	Stibogluconate or meglumine 20 mg/kg/day IV × 10 days[14]	
Visceral*	Liposomal amphotericin 3 mg/kg/day IV once daily days 1-5, then day 14 and 21[14] WHO regimen: 10 mg/kg IV on 2 consecutive days[14]	Stibogluconate or meglumine 20 mg/kg/day IV once daily × 28 days *or* miltefosine 2.5 mg/kg PO qd × 28 days[14]
Dogs	Sodium stibogluconate (Pentostam) 30-50 mg/kg IV/SC q24h × 30 days (available through CDC)	Allopurinol 10 mg/kg PO q8h × 3-24 months (long-term maintenance), works best when combined with amphotericin B 0.25-0.5 mg/kg IV q48h until total cumulative dose of 5-10 mg/kg
Cats	Pinnectomy	Meglumine antimoniate 5 mg/kg SC with 10 mg/kg ketoconazole PO, 4-wk course followed by no therapy for 10 days, repeated three times (used successfully to treat cutaneous lesions in one cat)[15]
Horses	Observation for lesion resolution, pinnectomy	

*Management complex; resistance varies by region; infectious disease consultation recommended.

Treatment

Treatment in humans may involve an often prolonged course of treatment with a variety of agents. The medical management of leishmaniasis is complicated and drug resistance varies by region; therefore infectious disease consultation is advisable. Table 9-38 outlines some currently recommended therapeutic regimens.[14]

In dogs, no drug has been consistently curative. Relapses and the repeated need for treatment are common, although maintenance therapy can reduce parasitemia and reduce the likelihood of transmission.[10]

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LEPTOSPIROSIS

Peter M. Rabinowitz and Lisa A. Conti

Leptospirosis ictohemorrhagica (ICD-10 A27.0), Other forms of leptospirosis (A27.8)

Other names in humans: Weil's disease, mud fever, swamp fever, rice field fever, swineherd disease

Other names in animals: redwater of calves, moon blindness (ophthalmia periodica) of horses, Stuttgart disease, canicola disease in dogs

Although leptospirosis is considered a rare disease in the United States, it is one of the most prevalent and important zoonotic diseases worldwide.[1] The epidemiology of this emerging infection appears to be changing due to climate and manmade alterations in the environment. Contamination of water supplies by infected animals is a major source of human exposure, underscoring the importance of waterborne infectious disease risks. The occurrence of leptospirosis in dogs and wildlife living near human habitation and the fact that it is capable of causing both serious disease and outbreaks among groups with high-risk exposure argue for greater awareness of this disease among human and animal health professionals.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide descriptive epidemiology of the disease in animal and human populations.
- Educate the public on modes of transmissions (e.g., do not allow animals to drink from contaminated water bodies, maintain good hygiene at kennels and in livestock birthing areas, control rodents).
- Support rodent control efforts in the community.
- Educate local veterinary and human health clinicians in endemic areas about prevention strategies targeted to groups at risk.
- Educate occupational health providers regarding risk groups and how to recognize signs and symptoms of disease.
- Ensure that workers at risk are using appropriate PPE.
- Disinfect with 1% sodium hypochlorite, 70% ethanol, glutaraldehyde, detergents and acid. The organism is killed by pasteurization and moist heat (121° C for 15 minutes).[2]

Human Health Clinicians

- Screen patients for occupational, recreational, housing, and animal (pet and livestock) exposures.
- Treat and report cases to health department if reportable in state.
- Counsel patients on measures to reduce risk of transmission to other humans (direct transmission is rare but possible; e.g., during sexual intercourse and breastfeeding) and from animals (e.g., hygiene regarding urine, reduce rodent exposure).
- Ask patients/family members about any observed illness in pets or other nearby animals; communicate with veterinary professionals animal cases are suspected.
- Counsel immunocompromised patients about risks from animal and environmental contact.

- No human vaccine is available in the United States.
- Exposure prophylaxis: In evaluating an individual who has been exposed to leptospirosis through occupational or environmental contact, consider antibiotics for prophylaxis. A systematic review concluded that prophylactic treatment with doxycycline 200 mg PO weekly for individuals at high risk of exposure (such as individuals training in jungle conditions during the rainy season) was superior to placebo in preventing cases of infection. (evidence-based recommendation: strength B).[3]

Veterinary Clinicians

- Segregate and treat infected animals.
- Vaccinate at-risk dogs and cattle and pigs. Vaccination does not protect against the carrier state. Annual vaccination in closed herds, semiannual vaccination in open herds.[4]
- Counsel owners and veterinary staff about ways to reduce zoonotic risks (precautions with animal urine and other body fluids) and symptoms of disease in humans, advise them to contact medical providers if suspect human cases.
- If veterinary staff experiences occupational exposure to infected animal, consult occupational or infectious disease provider regarding follow-up and possible antibiotic prophylaxis.
- If treating an infected pet, counsel family members regarding zoonotic risk and to contact their health care provider for further advice. Consider directly contacting the medical care provider, especially when immunocompromised patients are in the household or otherwise in contact with an animal case.
- Report animal cases to appropriate animal health authority if indicated in state.

Agent

Leptospirosis is caused by gram-negative spirochete bacteria in the genus *Leptospira*. Based on molecular analysis, there are believed to be at least 13 different species of *Leptospira* and more than 250 serovars.[5] These species and serovars vary widely in pathogenicity. Leptospires can be cultured in polysorbate-albumin media (Figure 9-72).[5]

Geographical Occurrence

Leptospirosis is considered an emerging infectious disease and one of the most common global zoonoses[1]; it is found worldwide except in the polar regions. It is highly prevalent in tropical countries with areas of high rainfall and alkaline soils.[6] The CDC has removed leptospirosis from the list of nationally reportable diseases, and estimates that 1 to 200 cases are identified yearly in the United States (50% of cases occur in Hawaii).[7] However, recent outbreaks and sporadic cases in the United States suggest that leptospirosis remains underdiagnosed and underreported in animals and humans, and that many U.S. health care providers are unfamiliar with the epidemiology and clinical presentation of this disease, which is capable of causing severe morbidity and (rarely) death.
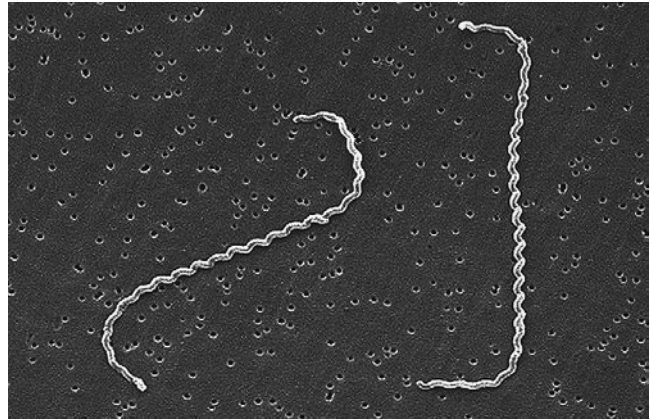

Figure 9-72 ■ Scanning electron micrograph of *Leptospira interrogans* showing helical structure and curved (hooked) ends (original magnification ×60,000). (From Mandell GL, Bennett JE, Dolin R (eds): *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2005, Churchill Livingstone Elsevier. Courtesy of Rob Weyant, Centers for Disease Control and Prevention, Atlanta, Ga.)

Groups at Risk

Leptospirosis is an important occupational disease risk for farmers, dairy and abattoir (slaughterhouse) workers, butchers, hunters, dog handlers, veterinarians, and other veterinary health providers who have direct contact with animals. Workers with exposure to contaminated water, such as military personnel, rice farmers, fishing industry workers, plumbers, and sewer workers, are also at risk.

Recreational exposure to contaminated water leads to infection in campers, sportsmen, freshwater bathers, and travelers returning from highly endemic countries. Urban slum dwellers with rodent exposure are another risk group and infection has been reported in children who handled infected puppies.[5] In the United States, recent reported cases have occurred among cleanup workers at a Hawaiian university campus where a stream had flooded,[8] a returning traveler who had explored caves in Malaysia,[9] an inner-city hospital patient who had recently swum in a creek,[10] and triathletes and community dwellers who had swum in and ingested water from a contaminated lake.[11]

HIV-infected and other immunocompromised patients are at risk of severe disease.[12]

Hosts, Reservoir Species, Vectors

Hosts who exhibit clinical infection with leptospirosis include humans, dogs (where the incidence is reported to be increasing),[13] horses, cattle,[14] sheep, and swine. *Leptospira* species appear to exist subclinically in a large number of wildlife species, including rats and other rodents, raccoons, opossums, reptiles, and frogs. However, in some wildlife species, such as sea lions, periodic epidemics of clinical disease can occur.[15] In the northeastern United States and Canada increasing rates of infection among reservoir hosts, such as skunks, raccoons, and squirrels, that are common in suburban settings has been reported.[16]

Mode of Transmission and Life Cycle

Leptospira enter the body through breaks in the skin or contact with mucous membranes (Figure 9-73). Humans are commonly infected by exposure to water, moist soil, or food contaminated by urine or secretions, or by direct contact with infected animals. Venereal transmission occurs in swine and has been suspected in humans.[17] Eating infected rodents or other animals can result in infection through mucous membrane contact. Direct person-to-person transmission has been reported between soldiers working in close proximity in swampy areas, and in relation to breastfeeding.[6]

Environmental Risk Factors

Outbreaks in humans and animals have been linked to heavy rains resulting in flooding, moist soils, and standing water. Other environmental risk factors include alkaline soils and alkaline freshwater, rodent infestation, and suburban encroachment on wildlife habitat. A case control study of dogs found that seropositive dogs were more likely to live in periurban environments.[18] Inner-city households with cats have been associated with a decreased risk of leptospirosis, possibly through a reduction in rodent exposure.[19]
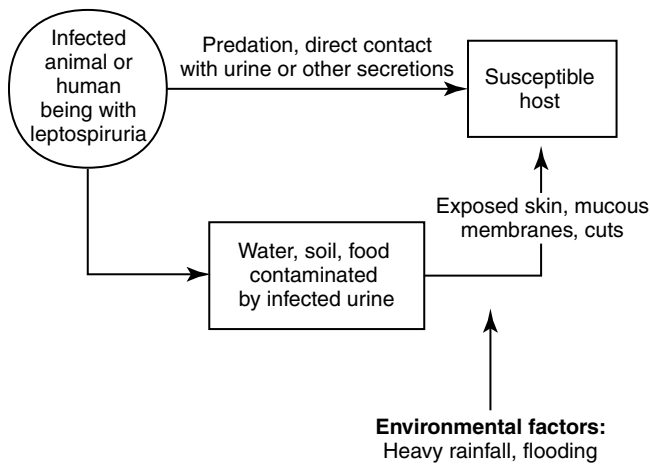
Disease in Humans

Leptospirosis in humans has protean manifestations, depending in part on the infecting serovar. Infection leads to a systemic vasculitis. The majority of human infections are mild and self-limited; however, in approximately 10% of cases, severe and even fatal illness can develop. The two main severe forms of the disease are Weil's disease (a triad of jaundice, acute renal failure, and bleeding) and severe pulmonary hemorrhagic syndrome (SPHS) (Table 9-39).

After the bacteria enter the body, there is an incubation period of approximately 10 days, followed by the abrupt onset of the leptospiremic phase or febrile phase, which can last 4 to 9 days. In addition to fever, conjunctival suffusion, uveitis, myalgias, and a pretibial rash can be seen. A convalescent (leptospiruric or immune) phase follows. During this period, which often lasts several weeks or longer, secondary transmission may occur through excretion of the leptospires in urine. Aseptic meningitis is a common occurrence during this phase of illness.[5] Figure 9-74 shows the biphasic nature of the illness.

Weil's disease may develop during the immune phase or progress directly from the acute phase of infection. Prominent features include renal failure caused by nephritis, hepatic dysfunction, and thrombocytopenia with hemorrhagic complications.

In some cases, hemorrhagic pneumonitis and severe respiratory distress leading to circulatory collapse can occur without hepatic or renal failure. Mortality is high in severe cases of Weil's disease and SPHS (Color Plate 9-40).

Figure 9-73 ▪ Life cycle of leptospirosis.

Table 9-39 ▪ Leptospirosis: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans	Exposure to fresh water, flooding, contact with animals	10 days (2-30)[22]	Acute onset of uveitis, conjunctival suffusion, myalgias, fever, renal failure, jaundice	Leukocytosis, liver, renal function test abnormalities
Dogs	Rural/suburban exposure to wildlife, peridomestic rodents, contaminated water	4-12 days[4]	Acute renal failure, fever, depression, lethargy, uveitis	Leukocytosis, renal and liver function test abnormalities, proteinuria, hematuria
Sheep	Rare, exposure to infected animals of other species		Lambs with more severe disease, fever, anorexia	
Horses	Exposure to contaminated urine, water, soil	2-8 months for chronic symptoms	Most asymptomatic[6] Uveitis (moon blindness), abortions	
Cattle			*Calves:* fever anorexia, dyspnea,[4] *Adults:* abortion, stillbirth, hemoglobinuria	
Pigs			Abortions, stillbirth	

Approximate time scale:	Week 1	Week 2	Week 3	Week 4	// Months-years //	Years
Incubation period	Acute stage	Convalescent stage			Uveitis ? interstitial nephritis	
2–20 days						
Inoculation	Fever					
Leptospires present in:						
Blood						
CSF					Reservoir host	
Urine				Convalescent shedder		
Antibody titers			Normal response			
High					Titers decline at varying rates	
Low			Early treatment	Delayed		
"Negative"		Anamnestic				
Laboratory investigations	Blood					
Culture	CSF					
		Urine				
Serology	← ① →	← ② →	③	④	⑤	
Phases	← Leptospiremia →					
	← Leptospiruria and immunity →					

Figure 9-74 ■ Biphasic nature of leptospirosis. The serology numbers refer to specimens taken at different phases of illness to either diagnose acute illness or document chronic or past infection. (From Mandell GL, Bennett JE, Dolin R (eds): *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2005, Churchill Livingstone Elsevier. Adapted from Turner LH: Leptospirosis, *Br Med J* 1:231, and reproduced from Levett PN: Leptospirosis, *Clin Microbiol Rev* 14:296, 2001, with permission of ASM Press.)

Disease in Animals

Although many cases of leptospirosis in dogs are subclinical and chronic, dogs can develop acute disease with fever, anorexia, jaundice, vomiting, and hematuria. Other features of infection can include injected mucous membranes, uveitis, and cough.[20] The most common serious complications in dogs appear to be acute renal failure, vasculitis, and hepatic dysfunction.[21] The disease is much rarer in cats, but similar clinical features to dog leptospirosis may be seen.[20]

Cattle and other livestock including sheep, pigs, and horses can develop either acute or chronic forms of infection. The acute form is more common in young animals and can include fever or respiratory involvement. Adult livestock are more likely to develop the chronic form of the disease and manifest infection as abortion or stillbirth.

The disease is often subclinical in wild animals including rodents. Seals and sea lions may have depression, fever, and abortion.

Diagnosis

The differential diagnosis in humans includes acute causes of fever and jaundice such as hepatitis and malaria. Leptospirosis should be suspected in a patient who presents with exposure risk factors and fever, uveitis/conjunctival suffusion, and abnormal liver and renal function test results. Leptospires can be cultured from blood and cerebrospinal fluid (CSF) during the acute phase of illness and in urine after the first week of illness. Most laboratory diagnosis of human leptospirosis is currently based on serology using the microagglutination test (MAT) or ELISAs. Antibodies develop after about 1 week of illness. The MAT has a high specificity for specific serovars. However, it may lead to underdiagnosis if a person is infected with an unusual serovar not well covered by the standard test. Serial serology titers are required to document seroconversion—a fourfold increase in titer is considered evidence of recent infection.[6] The use of PCR techniques for diagnosing human leptospirosis has been reported.[23]

In animals, the MAT and ELISA are also used; paired sera are preferred. Diagnosis can be affected by a history of immunization, and the results of serology must be interpreted with caution in vaccinated animals. A milk ELISA can be used on a single cow or for bulk tank sampling.

Exposure Prophylaxis

A study of antibiotic prophylaxis for soldiers during jungle military training showed a protective benefit of doxycycline, 200 mg/week, in preventing infection with leptospirosis.[24] Therefore individuals with high-risk exposures for short periods can consider such prophylaxis. However, the efficacy of prophylaxis in other situations, such as after exposure, remains unclear.

Treatment

Antibiotic treatment in people and animals is not always curative but should be started as early in the course of disease

Table 9-40 ■ Leptospirosis Treatment in Humans and Other Animals		
Species	**Primary Treatment**	**Alternative**
Humans	Penicillin G 1.5 million units IV q6h *or* ceftriaxone 1 gm q24h × 7 days	Doxycycline 100 mg IV/PO q12h *or* ampicillin 0.5-1 gm IV q6h[27]
Dogs	Doxycycline 5 mg/kg q12h PO/IV × 14 days	Penicillin G 25,000-40,000 units/kg q12h IM/SC/IV × 14 days *or* ampicillin 22 mg/kg PO/IV/SC q6-8h × 14 days *or* amoxicillin 22 mg/kg q8-12h PO × 14 days[20]
Swine	Tetracycline 800 gm/ton of feed × 8-11 days[26]	
Cattle	Tetracycline 40 mg/kg IM qd × 3-5 days, oxytetracycline[4,26]	Amoxicillin 15 mg/kg 1 or 2 (q48h) doses[26]

as possible because of a possible benefit (Table 9-40). Recommended agents include penicillin G, doxycycline, ceftriaxone, and amoxicillin. The serovar may affect the efficacy of the selected antibiotic. Supportive care may be indicated, and hemodialysis is correlated with improved prognosis in severe acute renal failure cases.[25]

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LYME DISEASE

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Lyme Disease (ICD-10 A69.2)

Other names in humans: Lyme borreliosis

Other names in animals: Lyme borreliosis, Lyme arthritis

Lyme disease is caused by a bacterial spirochete, *Borrelia burgdorferi,* and is the most commonly reported arthropod-borne human infection in the United States.[1] Lyme disease presents opportunity for collaboration between human and animal health practitioners. The increased environmental exposure of dogs to ticks, as well as the availability of routine in-house screening tests, has provided critical evidence of

the geographical incidence and prevalence of the infection in dogs that serves as a sentinel for human Lyme disease infection risk.[2] Although ticks are considered the principal vector for transmission of *Borrelia* species to humans and animals, there have been occasional published reports of the potential for transmission through blood, milk, placenta, or urine, but none of these alternative transmission routs has been confirmed by unambiguous culture results.[3] In addition to dogs, Lyme disease has been reported in cats, horses, cattle, and goats. Tick avoidance and tick control are important prevention measures for both humans and domestic animals. The risk of Lyme disease to humans and other animals is related to landscape change and human advancement on the habitat of local deer and rodent populations that maintain the vector tick *Ixodes scapularis* (formerly known as *I. dammini*). Therefore development of recommendations that focus on environmental factors associated with Lyme disease could decrease infection risk and benefit both humans and companion animals.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide descriptive epidemiologic analysis of this reportable disease and assessment of local Lyme disease risk for the health district.
- Educate the public to:
  - Avoid tick-infested areas, but if not possible, wear appropriate clothing (long sleeves, long pants, tuck pants legs into socks, and light-colored clothing to visualize ticks). Wash clothes with hot water.[4]
  - Use CDC-recommended tick repellents such as DEET, picaridin, or alternatives on clothes or bare skin following label instructions.
  - Do frequent tick checks to remove even tiny immature-stage ticks ("seed" ticks). Inspect children at least once daily for ticks. When in heavily infested areas inspect children every 3 to 4 hours.
  - Use appropriate technique to remove ticks. Wear gloves or grasp tick with tweezers as close to the skin as possible and pull gently (do not use a match, petroleum products, or nail polish). Follow up by cleaning the area, applying antibiotic topical on tick bite site, and washing hands.[5]
  - Implement integrated pest management techniques including landscape management (see Box 9-3). Counsel pet owners to discuss Lyme disease prevention strategies with their veterinarian.
- Work with local agencies to control deer and rodent populations.
- Work with local planning agencies on smart growth to avoid fractionating forested areas.

Human Health Clinicians

- Report Lyme disease cases to public health authorities using the case definition; see http://www.cdc.gov/ncphi/disss/nndss/casedef/lyme_disease_2008.htm.

- Counsel patients to avoid tick exposure and use appropriate tick repellents.
- Inquire about occupational risk factors for infection, and ensure that workers at risk are taking precautions.
- Understand that Lyme disease screening tests may provide false-positive or false-negative results and may require a confirmatory analysis at a reference laboratory such as the CDC.
- Become aware of Lyme disease prevalence through discussions with public health authorities.
- Ask patients about pet ownership generally. For those with pets who live in Lyme endemic areas or who may visit endemic areas, ask if they have discussed Lyme disease risk with their veterinarian.
- Judiciously use antibiotics; antibiotics may not be indicated as a prophylaxis for (nonengorged) tick bite alone.
- No vaccine for Lyme disease is currently commercially available for humans.

Veterinary Clinicians

- Educate clients and hospital team members about how to appropriately remove ticks. Have pet owners remove ticks as soon as possible, ideally before attachment. Conduct daily tick checks on dogs, preferably when coming in from outdoors, with particular attention to the head, ears, and warm fold areas (e.g., between toes, groin). Frequent brushing removes unattached ticks from pets that may be transferred to humans.
- In endemic areas, consider screening dogs with a Lyme C6 antibody test to diagnose subclinical dogs. Among infected dogs, 90% to 95% may be subclinical or have vague clinical signs that go unnoticed by owners.[3,6]
- Educate clients to treat dogs and cats preventatively with topical tick control.
- Consider vaccinating dogs that are at risk and in endemic areas annually against Lyme disease with an OspA Lyme vaccine (controversial).[3,6]

Agent

Lyme disease is caused by a number of species of gram-negative, spirochete bacteria belonging to the genus *Borrelia* (Figure 9-75). *Borrelia* species that cause Lyme disease are grouped under the name *Borrelia burgdorferi sensu lato*. In the United States, the predominant genotype associated with Lyme disease is *Borrelia burgdorferi sensu stricto*. This genotype also causes Lyme disease in Eurasia, as do *B. afzelii*, *B. garinii*, and *B. japonica* (Japan). Among these genotypes, there is considerable genetic diversity.[7] *Borrelia* are slow-growing bacteria (Figure 9-76) that require special culture medium and generally are difficult to culture from blood and tissue biopsies.[8] The organisms are sensitive to heat and ultraviolet light and do not survive long outside the body. Effective disinfectants include 1% sodium hypochlorite and 70% ethanol.[9]

Geographical Occurrence

Initially recognized in the Northeastern United States, specifically in Lyme, Connecticut, in 1975, Lyme disease
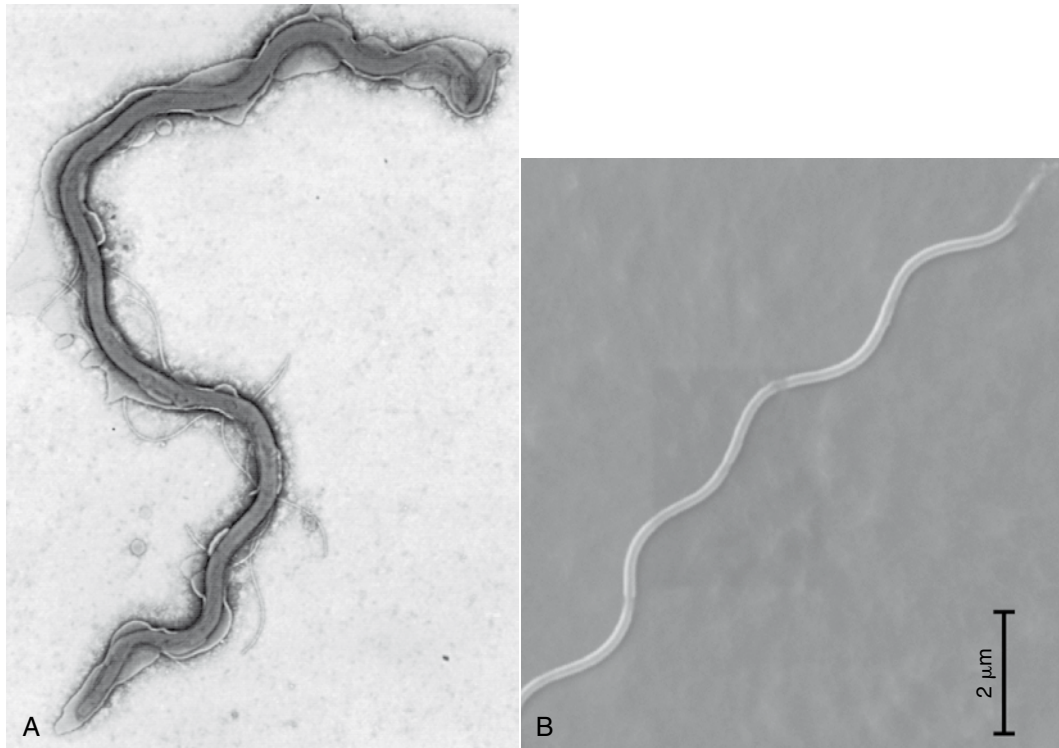
Figure 9-75 ■ **A**, Transmission electron micrograph of *B. burgdorferi* showing periplasmic flagella that have been released from the confines of the outer membrane secondary to specimen preparation (phosphotungstic acid, ×7100). **B**, Scanning microscopic view of *B. burgdorferi* (×15,000). (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy R. Straubinger, University of Leipzig, Leipzig, Germany.)
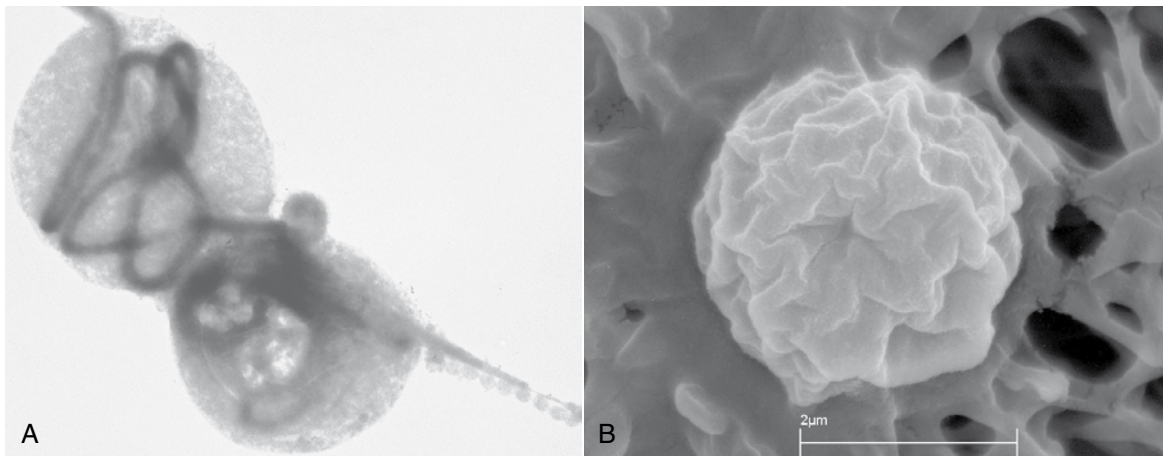

Figure 9-76 ■ **A**, Transmission electron microscopic (×12,000) and **B**, scanning electron microscopic (×12,000) appearance of cystic form of *B. burgdorferi*, a defense mechanism of organism for survival under adverse conditions such as antimicrobial therapy or host immune defenses. (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy R. Straubinger, University of Leipzig.)

has now been reported in almost every state and in Canada, although the tick vectors have a more restricted distribution. The distribution of Lyme disease in the United States is concentrated, with 12 states accounting for about 95% of reported human cases.[10] Clinical illness from *B. burgdorferi* was first documented in dogs in 1984.[11,12] Geographical foci of higher infection risk are found along the East Coast, Wisconsin, Minnesota, and parts of California and Oregon (Figure 9-77), particularly in peridomestic areas. Areas of endemic Lyme disease activity have been reported in Europe, Russia, China, and Japan.[8]

Reported cases of Lyme Disease – United States, 2007

One dot placed randomly within county
of residence for each reported case

Figure 9-77 ■ Distribution of Lyme disease cases in the United States (2007). (From Centers for Disease Control and Prevention: *Lyme disease statistics*. http://www.cdc.gov/ncidod/dvbid/lyme/ld_Incidence.htm.)

Figure 9-78 ■ The black-legged tick *Ixodes scapularis* (formerly *I. dammini*), one of the vectors for transmitting Lyme disease. This tick is very small and can easily go unnoticed when fixed to the skin in an unengorged state. (From Habif TP: *Clinical dermatology: a color guide to diagnosis and therapy*, ed 4, St Louis, 2004, Mosby Elsevier.)

Groups at Risk

The risk of Lyme disease varies among regions and is generally correlated to the abundance of host ticks that can carry the disease agent. Individuals at most risk for infection are those living in endemic areas of high vector tick density, with a large proportion of the ticks infected, and that are engaged in activities with increased time and exposure to vector ticks.[13] Behavioral factors including frequent outdoor activities such as hunting, camping, and hiking most likely play an important role in disease susceptibility.[14] Higher numbers of cases have been reported in children aged 5 to 14 years and adults aged 35 to 60.[15]

Hosts, Reservoir Species, Vectors

Principal tick vectors include the black-legged (or deer tick) *Ixodes scapularis* (formerly *I. dammini*) in the Northeastern and upper Midwestern United States (Figures 9-78 and 9-79), and *I. pacificus* (western black-legged tick) in the Western United States, as well as *I. ricinus* (Europe) and *I. persulcatus* (Asia).[13] Often, a tick carrying the B. burgdorferi spirochete is also coinfected with other pathogens including *Anaplasma* and *Babesia.* Ixodid ticks attach quickly and feed to repletion without changing hosts.

Wild rodents, including the white-footed mouse (*Peromyscus leucopus)* in the Eastern seaboard (Figure 9-80), and the dusky-footed wood rat (*Neotoma fuscipes)* and kangaroo rats *(Dipodomys californicus)* in the West, serve as disease reservoirs for Lyme disease, remaining persistently infected and capable of infecting naïve ticks. In the West, the life cycle is more complex; the spirochete is maintained in an independent enzootic cycle involving *I. spinipalpis* as the arthropod vector.[13] Lizards may function as reservoirs in some parts of the United States or be a "dilution host," reducing the vector infection prevalence in other areas.[16]

In the United States, the white-tailed deer (*Odocoileus virginianus)* is the preferred host for *I. scapularis* and helps maintain adult tick populations by serving as hosts for the adult ticks. Birds may introduce *I. scapularis* into previously nonendemic areas.[13] Adult male ticks tend to remain on deer, whereas adult females will engorge after mating to drop off and lay about 2000 eggs in the spring.

Humans and domestic animals are accidental hosts for *B. burgdorferi*. Dogs have an increased risk of Lyme disease exposure in endemic areas relative to humans, and this risk can be highly focal with seroprevalence rates as high as 50% to 90% in endemic areas, providing sentinel information for humans.[10] Cats appear to have significant exposure risks as well; a seroprevalence study in Connecticut found more than 45% of cats showed evidence of infection with *B. burgdorferi*, as well as a significant amount of coinfection with *Anaplasma phagocytophilum*; yet most cats did not show clinical signs.[17]

Mode of Transmission and Life Cycle

The life cycle of *B. burgdorferi* is related to the 2-year life cycle of the hard *Ixodes* tick vector. *Ixodes* ticks pass through larval, nymphal, and adult forms (Figure 9-81). To mature from one form to another, they must consume a blood meal. Eggs are laid in the spring and the larvae hatch in the summer. As they feed on the blood of vertebrates, the larvae can become infected with *B. burgdorferi*. After feeding, the larvae become less active and mature into nymphs by the following spring.[18] The majority of human cases occur in the spring and summer as a result of bites by nymphs that are active and seeking a blood meal to allow them to develop into adults.[8] Once they have fed, the nymphs develop into adults. The adult female lays eggs the following spring to continue the cycle. With every feeding, it is possible for a tick to become reinfected with *B. burgdorferi* and also coinfected with other pathogens such as *Babesia* and *Anaplasma*.

When an infected nymphal or adult tick initially bites an animal, it appears that it must remain attached and feed for about 24 hours for upregulation of spirochete outer surface protein C (OSP C) and transmission of organisms to take place. Peak transmission occurs after about 48 hours.[3,19]
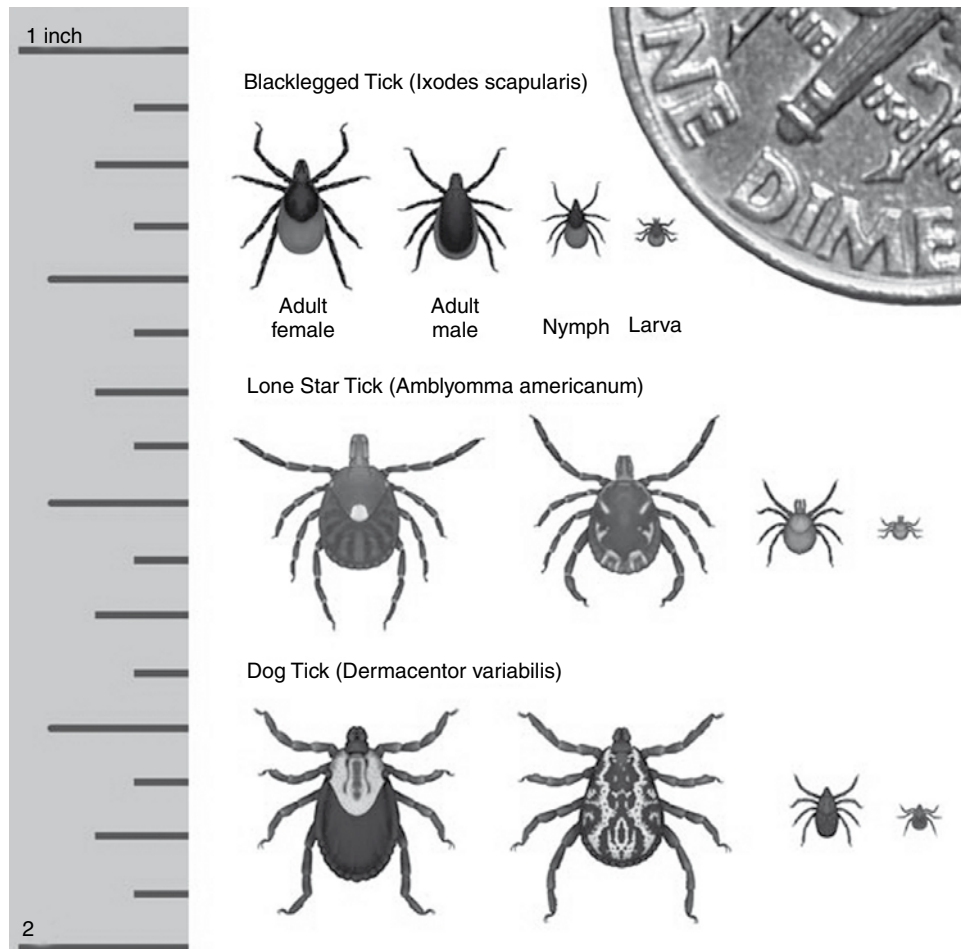
Figure 9-79 ▪ Relative sizes of these tick species. Only the black-legged ticks are known to transmit Lyme disease. (From Centers for Disease Control and Prevention: *Lyme disease transmission.* http://www.cdc.gov/ncidod/dvbid/lyme/ld_transmission.htm.)
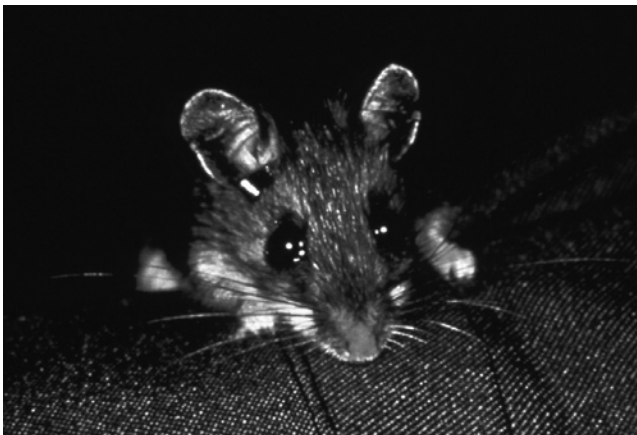

Figure 9-80 ▪ White-footed mouse, *Peromyscus leucopus*, a wild rodent reservoir host of ticks, which are known to carry the bacteria *Borrelia burgdorferi*, responsible for Lyme disease. During their larval stage, *Ixodidae,* or "hard ticks," feed on small mammals, particularly the white-footed mouse, which serves as the primary reservoir for *B. burgdorferi*. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

Environmental Risk Factors

The relation of environmental factors to the risk of Lyme disease is complex but it appears that landscape modification in the United States related to suburbanization of the human population is playing a significant role. As suburban developments and other human built environments encroach into land that was previously forest habitat, they produce "fragmentation" of forests (Figure 9-82). This breaking up of forested area into patches interspersed with human residential development has caused an increase in deer populations by providing ideal vegetative habitat (including ornamental shrubs for deer to eat) and reduced pressure of being hunted and predators. It also appears to favor increases in populations of peridomestic *Peromyscus,* which are important hosts for *Ixodes* ticks and for *B. burgdorferi*. Such forest fragmentation has been shown to be related to tick abundance and infection rates.[20] However, individual human behavior appears to play an important role in determining human risk, including time spent outdoors and use of protective repellents and clothing.
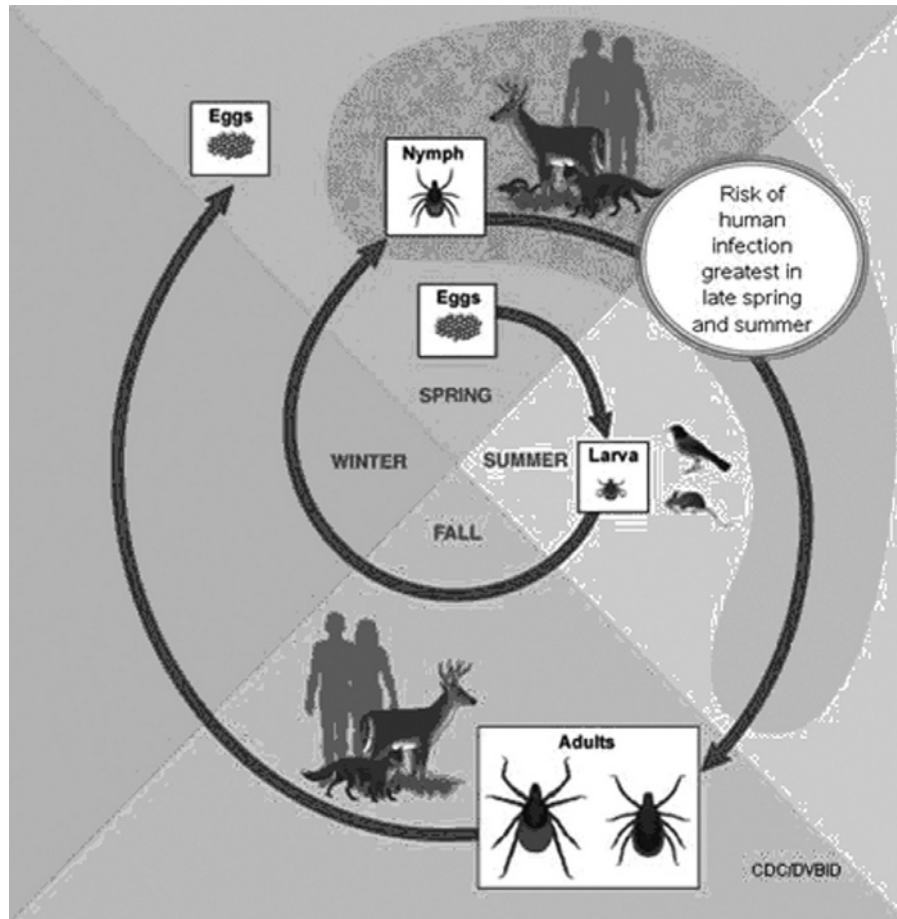
Figure 9-81 ■ Life cycle, Lyme disease. (Modified from Centers for Disease Control and Prevention: *Lyme disease transmission*. http://www.cdc.gov/ncidod/dvbid/lyme/ld_transmission.htm.)

Another environmental factor is climate and climate change. Warmer winters may result in increased tick abundance during the following spring and summer.[21] Because the environment appears to play a role in Lyme disease risk, studies have examined whether environmental modifications can reduce such risk. Area-wide acaricide use reduces tick populations, but many communities are reluctant to use wide-scale pesticides. However, targeting small areas of high human exposure,

Figure 9-82 ■ Suburban development and other human built environments encroach into land that was previously forest habitat. (From Centers for Disease Control and Prevention: *Learn about Lyme disease.* http://www.cdc.gov/ncidod/dvbid/lyme/index.htm.

such as residential yards, has been highly effective in reducing nymphal tick density.[22] Treating host animals with acaricides, such as the "four poster" method of treating deer with acaricide at feeding stations, has reduced tick populations, but the distribution of bait designed to reduce tick feeding on rodents is less effective. By eliminating the deer population, the maintenance host of ticks, the risk of Lyme disease has been nearly eliminated in an island setting.[23,24] Integrated pest management can be effective to aid in tick control, including landscape modification around dwellings (see "Key Points for Clinicians and Public Health Professionals").

Disease in Humans

In many of the reported cases, the disease begins with early localized infection, consisting of fever and a characteristic skin rash (erythema migrans [EM]) that often starts with a red macule or papule at the site of the tick bite that expands into a circular rash. The rash may develop central clearing, producing a bull's-eye appearance (Color Plate 9-41). The bacterium is sometimes cultured from the leading edge of the rash. Accompanying symptoms may include fatigue, fever, headache, anorexia, arthralgias, myalgias, and lymphadenopathy. Southern tick-associated rash illness (STARI), a differential in the early diagnosis of Lyme disease, manifests with a similar EM rash (Color Plate 9-42), mild clinical signs, and absence of antibodies to *B. burgdorferi*. STARI may be associated with *B. lonestari* rather than *B. burgdorferi* and transmitted by the lone star tick, *A. americanum* (see http://www.cdc.gov/ncidod/dvbid/stari/index.htm).

Days to weeks after the onset of the rash, early disseminated infection may develop, with more severe systemic symptoms. Multiple EM lesions may appear during this phase, as well as borrelial lymphocytomas—blue-red nodules on the earlobes or nipples. Early disseminated infection can involve the nervous system with the development of chronic symptoms including seventh nerve (Bell's) palsy or facial paralysis, meningitis, motor or sensory peripheral neuropathy, and encephalopathy. Cardiac involvement may occur with atrioventricular block. If infection remains untreated, late-stage disease can develop months to years after initial infection, with arthritis of the knees or other weight-bearing joints (Figure 9-83). In late-stage disease, the skin can develop acrodermatitis chronica atrophicans, erythematous plaques and nodules on the extremities. Other complications include encephalopathy and keratitis (Figure 9-84).[25] Previous infection does not confer immunity.

Disease in Animals

Most dogs do not manifest clinical signs after exposure to *B. burgdorferi* or have vague signs that go unnoticed by the owner. Dogs have not been reported to have the bull's-eye rash. Approximately 5% of seropositive dogs develop clinical Lyme disease.[6,26] Clinical signs may not appear for 2 to 6 months after infection and may include lameness, fever, anorexia, myalgia, lethargy, lymphadenopathy, cardiac arrhythmias (rarely), neurological signs, and ocular manifestations (Color Plates 9-43 and 9-44).[3,6] Dogs have also been reported with Lyme arthropathy, a recurrent arthritis with lameness particularly in the tarsal and carpal joints (Figure 9-85). Lyme nephropathy, a chronic protein-losing nephropathy that may
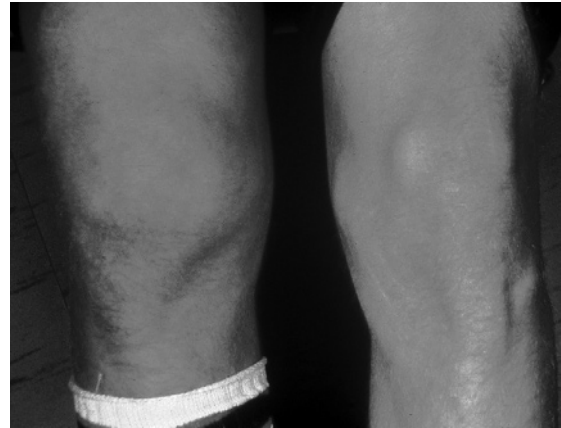

Figure 9-83 ▪ Inflammation involving knee joint in Lyme disease. (From Yanoff M, Duker JS: *Ophthalmology*, ed 3, St Louis, 2004, Mosby Elsevier. Adapted with permission of the American Academy of Ophthalmology: *Basic and clinical science course*, San Francisco, American Academy of Ophthalmology, 1998-1999.)
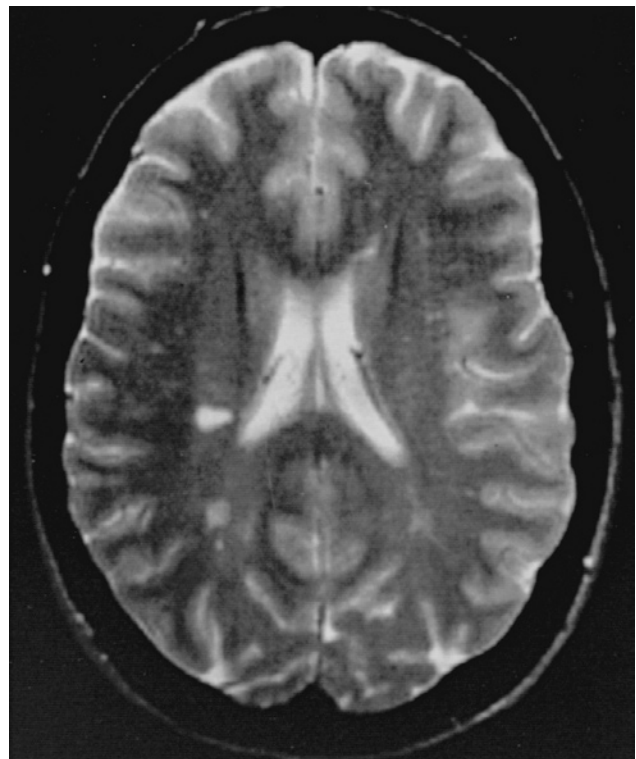

Figure 9-84 ▪ T_2-weighted magnetic resonance imaging scan in a patient with Lyme disease reveals areas of increased signal intensity in the cerebral white matter. (From Mandell GL, Bennett JE, Dolin R: *Principles and practice of infectious diseases*, ed 6, New York, 2005, Churchill Livingstone Elsevier.)

be related in part to immune complex deposition, can progress to a fatal acute oliguric or anuric renal failure.[6,26] Some have questioned whether the nephropathy could be related to coinfections with other agents. Coinfection with other tick-borne diseases is common, either transmitted by the same tick vector (*A. phagocytophilum*, *Babesia microti*, or *Bartonella* species) or other tick vectors (*Ehrlichia* species and *Rickettsia rickettsii*).[3,6] Previous infection with *B. burgdorferi* does not appear to confer immunity.

Figure 9-85 ■ Experimentally induced borrelial arthritis in the thoracic limb of beagle dog. Fever and shifting leg lameness develop 60 to 90 days after inoculation. Lameness occurs earliest and is most severe in the limb closest to the inoculation site. (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy R. Straubinger, University of Leipzig.)

Cats appear to be largely asymptomatic but can rarely develop arthritis.[27]

Serosurveys using ELISA antibody screening have reported seroprevalence rates in horses greater than 80% in endemic areas.[28] Although a wide range of clinical conditions have been associated with Lyme infection in horses, clinical infection is considered to be extremely rare and poorly understood.[29] EM lesions have been experimentally caused by infecting rabbits with *B. burgdorferi*. Table 9-41 provides a comparison of Lyme disease clinical presentations in humans and other animals.

Diagnosis

In humans who present with a classic EM rash (described as 5 cm or greater to differentiate it from a hypersensitivity reaction) and a history of a tick bite or tick exposure in a Lyme-endemic area, serological confirmation may not be necessary. However, a search should be performed for possible coinfection with agents such as *Anaplasma* and *Babesia*. When the rash is not present but Lyme disease is suspected and pretest probability is 20% or greater, serological testing using a two-step method is recommended. This consists of a screening ELISA test followed by a confirmatory Western blot if the ELISA is indeterminate or positive. If less than 4 weeks has elapsed since the onset of infection, both IgG and IgM should be tested; if more than 4 weeks have elapsed, only IgG should be tested. The two-step method is considered to have high specificity and a low risk of false-positive diagnosis.[31,32]

In animals, a rapid antibody test has been developed to detect antibodies against the C6 *B. burgdorferi* protein and correlates well with the Western blot immunoassay.[33] This test detects only antibodies against antigen acquired through natural exposures, and therefore will not yield positive results in vaccinated animals.[6] In dogs, testing validates exposure to the *B. burgdorferi* organism but not clinical illness. Supporting evidence for a diagnosis of Lyme disease is based on history of exposure to *B. burgdorferi* through exposure to *Ixodes* ticks in an endemic area, clinical signs, positive C6 peptide and/or Western blot antibody test results, ruling out other differential diagnoses, and response to antibiotics.[6]

Controversy exists in the veterinary literature about whether healthy dogs should be routinely screened for *B. burgdorferi* antibodies.[6] Limitations to serological testing include a long incubation period, presence of subclinical infections, cross-

Table 9-41 ■ Lyme Disease: Comparative Clinical Presentations in Humans and Other Animals				
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**	**Diagnostic Findings**
Humans	Tick exposures	Days to weeks	Early localized form: EM skin lesion, fever *Early disseminated infection:* paralysis of facial muscles, meningitis, numbness in arms or legs *Late-stage infection:* arthritis, cardiac pathology, neuropathy	Positive serology, direct immunofluorescence, rarely isolation from skin biopsy
Dogs	Tick exposures Younger dogs appear to be more susceptible than older dogs, coinfection with other agents	2-5 months in experimentally infected dogs[30]	Often subclinical Arthritis, anorexia, and depression, cardiac disease, nephritis, lymphadenopathy[27]	C6 *Borrelia burgdorferi* ELISA (both qualitative and quantitative) and Western blot antibody test Antibodies generally can be detected 3-5 wk after experimental infection in dogs[6]
Cats	Tick exposures	4-6 weeks	Usually subclinical; fever, arthritis may occur	C6 *B. burgdorferi* ELISA and Western blot antibody test
Horses	Tick exposures	Weeks to months	Fever, lameness, Bell's palsy	Antibodies generally take 4-6 wk to develop in horses; immunoblots may not become positive until 10-12 wk in horses, skin biopsy

ELISA, Enzyme-linked immunosorbent assay; *EM*, erythema migrans.

reactions with other spirochetes, and persistence of antibody titers for months. A positive serological result in the presence or absence of clinical signs should alert the clinician to also search for coinfections commonly associated with *B. burgdorferi* exposure, including *Anaplasma, Babesia, Ehrlichia, Rickettsia, Bartonella, Leptospira, Mycoplasma,* and *Neorickettsia*.[6,10] Clinically normal dogs with positive serological findings should have follow-up by a veterinarian with semiannual or annual health examinations, be monitored for proteinuria, and the owner should be alerted to contact the veterinarian if any clinical signs of Lyme disease develop.

Treatment

Management of *B. burgdorferi* infection in humans and animals involves the use of antibiotics for treatment of disease. Prophylaxis with oral doxycycline may be offered to adults or children if a tick bite is due to an adult or nymphal *I. scapularis* tick that has been attached for at least 24 hours, less than 72 hours has elapsed since removal of the tick, and the use of doxycycline is not contraindicated (doxycycline 200 mg PO for 1 dose; children 8 and older, 4 mg/kg).[1] Following a tick bite, regardless of whether prophylaxis is given, individuals should be monitored for any signs of disease such as development of a fever or an EM rash.

The use of antibiotics for disease treatment depends on the stage of disease. Table 9-42 outlines recommended antibiotics regimens outlined by the Infectious Diseases Society of America (IDSA). The use of macrolides should be reserved for persons who are unable to tolerate tetracyclines, penicillins, or cephalosporins because their efficacy may be lower.

Recommended antibiotic regimens for animals with clinical manifestations of Lyme disease are also shown in Table 9-42. More specific supportive and symptomatic medical treatment should be directed toward the affected organ system. Dogs do not appear to develop natural immunity to infection nor do they develop long-term immunity after vaccination. Therefore after the full course of antibiotic treatment, subsequent exposure to *B. burgdorferi* can result in reinfection.

In the United States there are currently four vaccines for dogs that stimulate antibody production against a single outer surface protein A (OSP A) located on the bacterium when it is attached to the tick's gut.[6] This prevents infection because the vaccinated dog's OSP A antibodies move with the blood to the tick's gut and bind to the bacteria, thus preventing the bacteria from upregulating OSP C and moving to the saliva to infect the dog.[34]

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Table 9-42 ■ Antibiotic Treatment of Lyme Disease in Humans and Other Animals

Species	Primary Treatment	Alternative Treatment
Humans (based on IDSA guidelines[1])		
Oral regimens: Early localized disease, isolated fifth nerve palsy, carditis (if only first-degree block), or arthritis without neurological signs	*Adults:* amoxicillin 500 mg PO tid, doxycycline 100 mg PO bid, *or* cefuroxime axetil 500 mg PO bid *Children:* amoxicillin 50 mg/kg/day (maximum 500 mg/dose) divided q8h, doxycycline if ≥8 yr 4 mg/kg/day divided bid (maximum 100 mg/dose), *or* cefuroxime 30 mg/kg/day (maximum 500 mg/dose) divided bid	*Adults and children:* consider selected macrolide if unable to tolerate penicillins, cephalosporins, or tetracyclines Monitor closely for resolution of clinical manifestations
Parenteral regimens: Lyme meningitis, other acute neurological manifestations, carditis	*Adults:* ceftriaxone 2 gm IV qd *Children:* ceftriaxone 50-75 mg/d IV (maximum 2 gm)	*Adults:* cefotaxime 2 gm, IV 8h *or* penicillin G 18-24 million units/day divided q4h IV *Children:* cefotaxime 150-200 mg/kg/day IV divided tid or qid, maximum 6 gm/day *or* penicillin G 200,000-400,000 units/kg/day, maximum 18-24 million units/day divided into doses q4h
Pregnant women	Same as nonpregnant but avoid doxycycline	
Dogs	Doxycycline 5 mg/kg PO q24h × 28 days[6]	Amoxicillin 20 mg/kg PO q8-12h × 28 days[27]
Horses	Doxycycline 10-20 mg/kg PO q12h[35]	Tetracycline 6.6 mg/kg IV qd[36]

IDSA, Infectious Diseases Society of America.

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LYMPHOCYTIC CHORIOMENINGITIS

Lynda U. Odofin

(ICD-9 049.0 Non-arthropod–borne lymphocytic choriomeningitis (ICD-9 049.0), Unspecified non-arthropod–borne viral diseases of central nervous system (ICD-9 049.9), Viral encephalitis NOS (ICD-10 A87.2)

Other names in humans: none

Other names in animals: none

Lymphocytic choriomeningitis (LCM) is a rodent-borne viral infection that may cause substantial neurological disease,[1,2] especially in immunocompromised individuals. Like other members of the Arenadiviridae family, the causative agent, lymphocytic choriomeningitis virus (LCMV), uses rodents as reservoirs.[3] Although the common house mouse, *Mus musculus,* is the natural host and principal reservoir of LCMV,[4] wild, pet, and laboratory rodents (rats, guinea pigs, hamsters) can be infected also. Infected mice can shed the virus throughout their lives[4]; infected females transmit the virus to their offspring, which may become asymptomatic persistent viral shedders.[5] Human infection is through contact with infected pet rodents or infected wild mice or their droppings. Infected rodents often do not show any signs of illness.[6] LCMV is an emerging neuroteratogen, known to cause diverse congenital

defects in children. In addition, because of recent outbreaks in organ transplant patients,[7-9] LCM is a reportable disease in some U.S. states; such states require physicians to report the disease to local health authorities.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Recommend that LCM be reportable in all states.
- Provide descriptive epidemiologic analysis of disease in the community.
- Investigate new cases of disease to determine the source of infection. Search home, place of employment, and immediate surroundings for presence of house mice. Test rodents, including pets found on such premises, for virus.
- Trace the source of infected pets. Work with pet stores to ensure all rodents sold are LCMV free.
- Recommend rodent-proofing homes:
  ○ Seal rodent entry holes or gaps with steel wool, metal lath, or caulk.
  ○ Trap rats and mice using appropriate snap trap.
  ○ Clean rodent food sources and nesting sites.

- Take precautions when cleaning rodent-infected areas:
  - Use cross-ventilation when entering a previously unventilated enclosed room or dwelling before cleanup.
  - Use rubber, latex, vinyl, or nitrile gloves.
  - Do not stir up dust by vacuuming, sweeping, or any other means. Instead, thoroughly wet contaminated areas with a bleach solution or household disinfectant. Hypochlorite (bleach) solution: mix 1½ cups of household bleach in 1 gallon of water. Once everything is wet, take up contaminated materials with damp towel and then mop or sponge the area with bleach solution or household disinfectant.
  - Spray dead rodents with disinfectant and then double-bag along with all cleaning materials and dispose of bag in an appropriate waste disposal system.
  - Remove gloves and thoroughly wash hands with soap and water (or waterless alcohol-based hand rubs when soap is not available and hands are not visibly soiled).
- Counsel people about appropriate rodent pet handling and care:
  - Wash hands with soap and water after handling pet rodents; use waterless alcohol-based hand rubs when soap is not available.
  - Keep rodent cages clean and free of soiled bedding.
  - Clean the cage in a well-ventilated area or outside.
  - Wash hands thoroughly with soap and water after cleaning up pet droppings. Closely supervise young children, especially those younger than 5 years, when cleaning cages, and make sure they wash their hands immediately after handling rodents and rodent caging or bedding.
  - Do not kiss pet rodents or hold them close to the face.
- Recommend that testing for LCMV should be included in the screening protocols for potential organ donors.

Human Health Clinicians

- Ensure that potentially exposed immunocompromised persons and pregnant women are given immediate medical attention, and advise such individuals to avoid contact with rodents and rodent droppings and to rodent-proof their homes.
- As part of the history, patients with aseptic meningitis and encephalitis should be asked about contact with rodents or rodent droppings.[10]
- Consider the diagnosis in all patients with rodent contact, such as pet owners, laboratory workers, and people from endemic areas. Work closely with respective state health department to discuss forwarding of samples on patients with disease suggestive of LCM to state laboratories or CDC for testing. (Testing for LCMV infection in asymptomatic persons is not necessary.)
- Consider LCMV infection in organ transplant recipients with unexplained fever, hepatitis, or multisystem organ failure.[10]

- Consider the diagnosis in patients (especially children) presenting with ocular scars regardless of no history of LCM. There have been reports from Europe about such cases.
- Report suspicion of disease immediately to public health authorities. LCM is reportable in some U.S. states.
- Discourage immunocompromised individuals, pregnant women, and families with children younger than 5 years from owning rodent pets. Also educate these individuals and parents about the consequences of owning pet rodents.[11] Consider routine testing of exposed pregnant women for the virus.
- If caring for occupational groups at risk, ensure that they are educated about symptoms of the disease, potential routes of transmission, use of adequate protective equipment, and that efforts are taken to reduce the risk of infection.
- Educate patients on reduction of environmental exposure risk through the elimination of wild rodents. Seal up rodent entry holes or gaps with steel wool, metal lath, or caulk.
- Trap rats and mice by using an appropriate snap trap. Clean up rodent food sources and nesting sites and take precautions when cleaning rodent-infected areas.[11]
- Promote proper handwashing after pet handling, and educate patients on providing a clean environment for pet rodents, such as supplying fresh bedding, food, and water on a regular basis. Clean cages outdoors or in well-ventilated areas.[11]
- Provide an information sheet on LCM prevention and control for at risk patients; a CDC information sheet is available at http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/lcmv.htm.

Veterinary Clinicians

- Advise clients to consult their physicians if an infected rodent is seen or if they are considering acquiring a rodent as a pet.
- Although the length of LCMV infection in pets varies, it has been shown that hamsters (subfamily Cricetinae) can transmit the virus for at least 8 months. Thus it is advisable to euthanize infected rodents.
- Although LCMV is not reported in animals, it is advisable to report increased incidence of cases to the local health authorities. Disease in animals may serve as an early warning of environmental exposure risk and possible human outbreaks.
- Screening pet rodents is not recommended as serological testing on rodents can be inaccurate and results misleading; however, hygienic practices (handwashing, cage sanitation) should be followed.[12]

Agent

LCMV is an enveloped single-stranded RNA virus belonging to the family Arenaviridae. The virus is serologically related to Lassa, Machupo, Junin, Guaranito, and Sabia viruses[5] and has been referred to as the prototypic member of the family. Along with Lassa and Lassa-related viruses,

LCMV forms the Old World group of the Arenaviridae.[13] Because of its unique properties, the LCMV model has been used to make important contributions to the fields of virology and immunology[14] and further understanding of viral-immune interactions. For instance, a specific glycoprotein (GP1), which is expressed on the envelope of LCMV,[15] mediates attachment of the virus, thereby initiating infection; thus mutations in this protein have the potential to alter viral targeting and influence the course of disease.[14] The immune system plays a major role in the outcome of human LCMV infection, ranging from no disease in healthy individuals to severe neurological disease in immunocompromised individuals.

Geographical Occurrence

LCMV is found worldwide and is endemic in wild mice. The virus has the greatest geographical range potential of any arenavirus and may occur on all land masses where the genus *Mus* has been introduced, including all continents except Antarctica.[7,16] The CDC estimates 5% of the U.S. wild mouse population is infected with LCMV, although epidemiological studies have documented a prevalence ranging from 3% to 21% in various U.S. locations.[11] An overall prevalence rate of 9% (43/468) was determined in wild mice captured in various sites, including residential and park locations in Baltimore, Maryland.[13]

In general, human infection, with the exception of those associated with hamsters,[13] tends to reflect the distribution of house mice.[17-19] Several serological studies conducted in urban areas have shown that the prevalence of LCMV infection among humans ranges from 2% to 5%.[11] In Baltimore, LCMV antibodies were found in 4.7% of 1149 inner-city residents tested,[6,20] and 49% of these reported house mice within their residence.[21]

The true incidence of LCM is unknown because many cases go unreported owing to the self-limiting effect in healthy individuals and lack of recognition by physicians.

Groups at Risk

In general, people who are in contact with rodents are at risk from LCMV infection; these include laboratory workers who routinely work with LCMV and laboratory mice and other rodents, farmers who are in frequent contact with wild mice, homeowners with mouse infestations, veterinarians who handle sick hamsters and other rodents, pet-store keepers, and pet rodent owners. Immunocompromised individuals, children younger than 5 years, and fetuses are particularly vulnerable to LCMV, which usually lead to severe infection in these subpopulations.

Recently LCMV infection has been associated with organ transplants.[8,9] Transmissions of virus between donors and recipients have been documented in the United States and other parts of the world. In one of these cases, the donor had recently acquired a pet hamster.[22]

Hosts, Reservoir Species, Vectors

LCMV has a highly restrictive host range; the house mouse (*M. musculus*) is the natural host and reservoir. Once infected, house mice often become lifelong shedders of the virus. Infection has also been reported in other rodents such as wood mice (*Apodemus sylvaticus*) and yellow-necked field mice (*A. flavicollis*).[23] Pet hamsters and guinea pigs are not known to be natural reservoirs for LCM, but pet rodents can become infected if they have contact with wild house mice in a breeding facility, pet store, or home. The golden hamster (*Mesocricetus auratus*) has become an important linkage host for LCMV transmission in humans and has been the source of recent outbreaks in the United States and abroad.[24-27]

Mode of Transmission and Life Cycle

Infected house mice play a major role in maintaining the life cycle of LCMV, thereby ensuring its persistence in nature (Figure 9-86). Wild mice are usually infected in utero, thereby
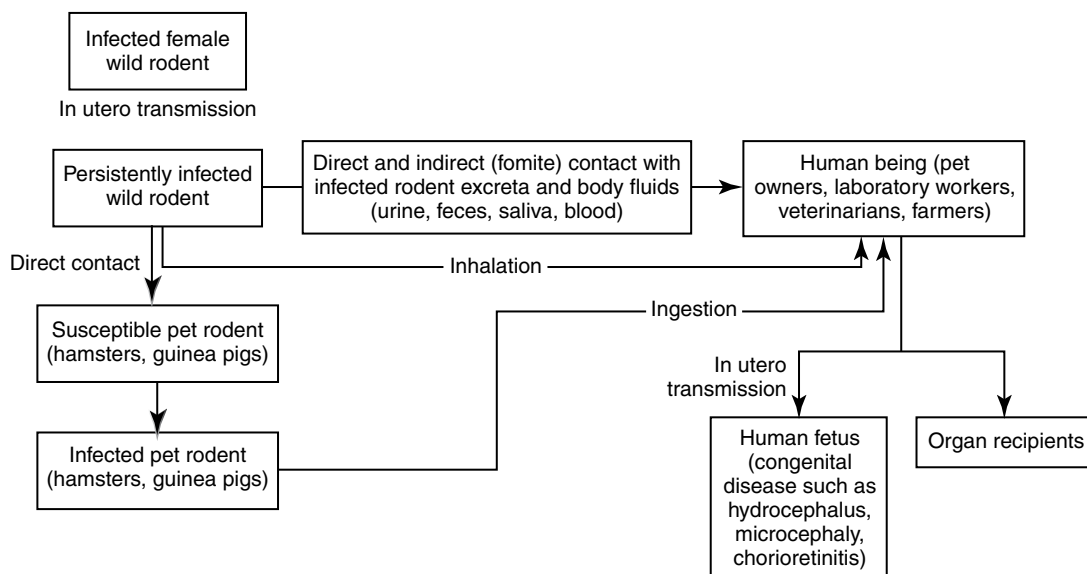

Figure 9-86 ■ Transmission cycle of lymphocytic choriomeningitis virus.

becoming chronically or persistently infected. The virus is usually excreted in urine, saliva, and feces of infected mice; transmission to humans occurs through the oral and respiratory contact with virus-contaminated excreta, food, or dust or through the contamination of skin lesions and cuts. Fomites such as bedding materials and other articles contaminated by infected rodents can put nearby humans at infection risk.

Human-to-human transmission occurs vertically between infected mother and fetus and horizontally from organ transplant between infected donors and recipients. Many of the women who gave birth to children with congenital LCM had a known exposure to wild mice or sick hamsters during pregnancy.[28]

Environmental Risk Factors

Most of the human LCMV infection is usually associated with contact with infected rodents (wild and pet rodents); thus the virus persistence in the environment is dependent on the infection rate of mice and frequency of contact between infected rodents and humans. For instance, during the fall there appear to be more mice in residential areas and even commercial areas such as restaurants because the mice look for warmer places to spend the winter. This enables more contact with nearby pet rodents (hamsters, guinea pigs) and even humans.

Disease in Humans

The immune response plays a major role in determining the manifestation and progression of clinical symptoms following LCMV infection. Thus infection in healthy people usually goes unnoticed and the virus is readily cleared. The onset of symptoms in ill individuals occur 8 to 15 days after exposure and is characterized by a biphasic febrile illness. The initial phase, which may last as long as a week, typically begins with any or all of the following flulike symptoms: fever, malaise, lack of appetite, muscle aches, retroorbital headache, nausea, and vomiting. Other symptoms that appear less frequently include sore throat; cough; arthritis; pain in the chest, testicles, and parotid gland; and rarely a rash. Most people recover after this phase. However, some may proceed to the second phase of the disease consisting of symptoms of meningitis or characteristics of encephalitis. The course of the disease is usually short, rarely fatal (about 1% mortality rate), and the prognosis is usually good, although convalescence with fatigue and vasomotor instability may be prolonged. An association between LCMV infection and myocarditis has been suggested.

Immunosuppressed patients such as organ recipients may develop fatal hemorrhagic fever; of 11 organ recipients described in three LCM clusters, 10 died of multisystem organ failure, with LCMV-associated hepatitis the prominent feature.[10]

Congenital LCMV infection first was recognized in Europe half a century ago.[24,29-31] The first U.S. cases were reported in 1993[30,31] and were characterized by severe brain and retinal injury.[15,32-35] Infection of the fetus during the early stages of pregnancy may lead to developmental deficits that are permanent; congenital LCM can be manifested in a variety of neurological signs such as microcephaly, chorioretinitis, hydrocephalus, seizures, and hypertonia (Figure 9-87). These signs are usually evident within 48 hours of birth. Diverse clinical signs have been recorded among 20 children diagnosed with congenital LCMV infection.[36] LCMV was diagnosed in these children at birth with follow-up of 11 years. Clinical signs covered a wide spectrum of neurological disease, but chorioretinitis was the only common presenting sign. In addition, the study suggested that the variability of the disease was related to the gestational timing of infection.

The most common laboratory abnormalities are leukopenia and thrombocytopenia in the first phase of disease with a mild elevation in liver enzymes in the serum. After the onset of neurological disease, an increase in protein levels and the number of white blood cells or a decrease in the glucose levels in the CSF is usually observed. No chronic state has been reported in humans, who usually clear the virus after the acute phase of the disease.
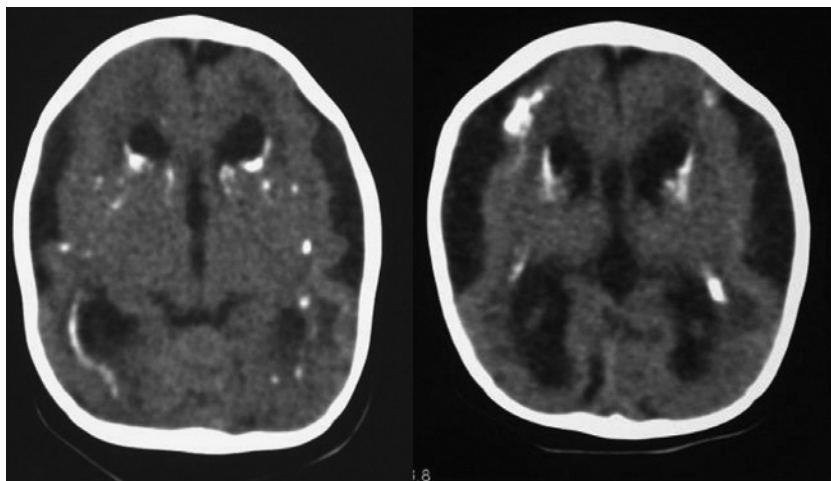

Figure 9-87 ■ Computed tomography at 5 months of an infant with profound developmental delay and chorioretinitis due to intrauterine lymphocytic choriomeningitis virus infection. The scan shows microencephaly, lissencephaly, and calcifications that are periventricular, intracerebral, and over the convexities of the brain. (From Long SS, Pickering LK, Prober CG: *Principles and practice of pediatric infectious diseases*, ed 3, Philadelphia, 2008, Saunders Elsevier. Courtesy G.L. Rodgers and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, Pa.)

Disease in Animals

Wild mice infected with LCMV in utero or at an early age develop a persistent subclinical infection and likely shed the virus for life. In naturally infected colonies of wild mice, the proportion of mice with persistent infection increases over time and at 4 years almost all the animals will be shedding virus.[37] Although most rodents with LCMV infection are subclinical, there have been reports of illness in infected hamsters characterized by a wasting disease that may run a long course (ranging from several weeks to months). Early signs include loss of activity, loss of appetite, and rough coat. Later the animal may show signs of weight loss, hunched posture, inflammation of the eye lids (blepharitis), clonic convulsions, and eventually death. The effects of LCMV have been studied in laboratory mice and mimic the disease in humans. Mice exposed to the virus at an older age are more likely to develop clinical disease. Gross lesions include necrosis of the liver and lymphoid tissue. LCMV infection has been documented in other animals such as dogs and monkeys; however, this is rare and has been consistently associated with contact to infected rodents.

Diagnosis

In humans, the early stage of disease could be confused with the flu, and at latter stages it must be differentiated from other aseptic meningitides and viral encephalitides, such as those caused by enteroviruses, the arthropod-borne togaviruses, or herpes simplex virus. Drug-induced meningitis is also a differential. In the case of congenital LCM, valid differential diagnoses include TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis), parvovirus, and enterovirus. Confirmatory diagnosis usually is by virus isolation in blood or CSF, by PCR, or identification of anti-LCMV IgM and IgG by ELISA or complement fixation. Detection of rising antibody titers in paired sera by IFA, and LCMV antigens by immunohistochemistry in liver biopsy or at autopsy also are considered diagnostic.

In rodents, confirmatory diagnosis is by viral isolation via inoculation in guinea pigs or LCM-free mice, complement fixation, and fluorescent antibody (Table 9-43).

Treatment

Early diagnosis is the key to successful treatment of LCM. Treatment is mainly supportive and involves use of antiinflammatory drugs. As for other cases of aseptic meningitis, suggested treatment regimens include intravenous fluids and analgesics.[38]

Treatment in animals is normally not advocated because they could develop a chronic state and continue to shed the virus, thereby posing a risk for other animals and humans. In general, by the time clinical signs are seen the prognosis is poor.

Table 9-43 ■ Lymphocytic Choriomeningitis: Clinical Presentations in Humans and Other Animals				
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**	**Diagnostic Findings**
Humans	Rodent exposure, immunocompromised	8-13 days; 15-21 days until meningeal symptoms appear[5]	*Adults:* flulike symptoms, myalgia, retroorbital headache, orchitis, parotiditis, arthritis, myocarditis, muscle ache, acute hydrocephalus, occasional rash[5] In rare cases, muscle weakness, paralysis, body sensation changes *Newborns/infants (0-<2 yr):* hydrocephalus, chorioretinitis, seizures, irritability, microcephaly, blistered skin, hypertonia, hypotonia, light perception, blindness, spastic quadriparesis, quadriplegia, hearing loss, cognitive deficits *Children (2-11 yr):* same as in infants, and ataxia, spastic diplegia	*Early stages of disease:* isolation of virus from blood or CSF by PCR or intracerebral inoculation of LCM-free mice (3-5 weeks old) or by cell culture[5] Demonstration of anti-LCMV IgM and IgG in serum or CSF by ELISA or complement fixation; Also demonstration of rising titers by IFA in paired sera Liver biopsy and multiple autopsy specimen stained positive for LCMV antigens by immunohistochemistry
Organ recipients	Infected organ donor	2-4 wk after transplant	Lethargy, anorexia, fever, shock, hepatitis, multisystem organ failure	
Rodents (hamsters, guinea pigs, mice)	Exposure to infected animals	Varies (several weeks to months)	Weight loss, ocular and nasal discharge, hunched posture, inflammation of the eyelids, clonic convulsions	Virus isolation by inoculation of LCM-free mice or guinea pigs, complement fixation, and fluorescent antibody on serum; immunofluorescence test on liver tissue

CSF, Cerebrospinal fluid; *LCM,* lymphocytic choriomeningitis; *LCMV,* lymphocytic choriomeningitis virus.

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METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTION

Peter M. Rabinowitz and Lisa A. Conti

Staphylococcal infection, unspecified (ICD -10 A49.0)

Other names in humans: MRSA

Other names in animals: MRSA

In recent years, methicillin-resistant *Staphylococcus aureus* (MRSA), long considered a nosocomial infection of hospitalized patients, has emerged as a significant pathogen in the community setting. Although *S. aureus* most commonly causes skin and soft tissue infections, invasive strains of MRSA have been associated with necrotizing pneumonia, sepsis, and necrotizing fasciitis, even in previously healthy persons.[1] This community-acquired MRSA (CA-MRSA) has also been found in companion animals[2-13] and livestock,[14-17] and there is evidence of transmission between animals and humans.[4,8,12,15,18-26] Concern has been expressed in the media about the emergence of a new "superbug" in people and animals. The picture is complex and evolving, reinforcing the need for close cooperation and communication between human and veterinary health professionals.

Public Health Professionals

- Provide descriptive epidemiology of infection in human and animal populations.
- Educate the public on prevention strategies, such as not sharing towels, clothes, or razors; frequent hand-washing (the Healthcare Infection Control Practices Advisory Committee has specific guidance), bandaging wounds, and disinfecting surfaces[27] (disinfectants include 1% sodium hypochlorite, glutaraldehyde, and iodone/alcohol combinations[28]); and the occurrence of carrier states.[29]
- Educate local veterinary and human health clinicians in risk areas and during high-risk periods about groups at risk and symptoms of disease.
- Educate health providers regarding risk groups and how to recognize clusters of patients.
- Ensure that workers at risk are using appropriate handwashing and PPE, as well as isolation of suspected cases.
- Encourage community members to be immunized against seasonal influenza as MRSA pneumonia can occur when healthy persons get influenza.
- Encourage and facilitate communication among physicians, veterinarians, and public health personnel.
- Ensure that positive aspects of animal contact are not ignored when assessing risk of zoonotic MRSA transmission.[30]

Human Health Clinicians

- Be alert to the possibility of MRSA when diagnosing and treating soft tissue infections.
- Treat and report cases to health department if reportable in state.
- Ensure that adequate hand hygiene practices are used with all patients and isolation procedures are used for suspected MRSA cases.[31]
- Counsel patients in whom MRSA has been colonized regarding measures to reduce risk of transmission to other humans and animals (bandage wounds, avoid direct contact).
- Query patients about animal contact. Ask patients/family members about any observed illness in pets.
- Consider the role of household pets and other animal contacts in situations where MRSA transmission appears to be ongoing in a household.[30] Recommend testing of pets only in situations where the entire household is being tested. All animal testing should be directed by the attending veterinarian, with results reported to the physician with pet owner consent.

Veterinary Clinicians

- Ensure that the clinical laboratory processing bacterial cultures is able to identify *S. aureus* and MRSA in clinical specimens.
- Isolate and screen all suspected cases. Isolate confirmed cases.
- Consider the role of household pets and other animal contacts in situations where MRSA transmission appears to be ongoing in a household. Recommend testing of pets in situations where the entire household is being tested. Animal results should be reported to the physician with pet owner consent.
- Ensure that adequate hand hygiene procedures and a high standard of environmental cleaning and disinfection are in place for staff in veterinary hospitals, and isolation procedures are used for suspected MRSA cases.
- Consider screening of veterinary personnel[32] during extreme circumstances (i.e., when there is epidemiological evidence of personnel-borne transmission and transmission persists after improvement in infection control practices are made). NOTE: The prevalence of MRSA colonization is higher in general among veterinary personnel than the general population[4,20,23,33] and veterinary staff can be exposed at any time. A negative screening result does not ensure that the person's test result will be negative the following day. A positive result also does not mean the person is involved in transmission, and there is no indication to restrict the duties of a veterinary worker in whom MRSA has been colonized.

Agent

The *S. aureus* bacterium is a gram-positive coccus that is coagulase positive and exists as a commensal organism in humans and many animal species, typically carried in the nasopharynx. The resistance of *S. aureus* to β-lactam antibiotics (penicillins and cephalosporins) including methicillin is due to the production of a penicillin-binding protein (PBP2a) encoded by the *mecA* gene, which is carried on a transposable genetic element called the staphylococcal *cassette chromosome mec* (SCCmec). There are at least five different SCCmec types (I-V) and several subtypes.[34] The PBP2a protein is expressed in the cell wall and has a low affinity for β-lactam antibiotic binding. Some MRSA also have membrane-bound protein pumps to remove antibiotics. Although strains of *S. aureus* that are resistant to methicillin have been identified for many years, some recent clones circulating in humans since 2000 include genes coding for Panton-Valentine leukocidin (PVL), a membrane toxin that appears to be related to virulence (Figure 9-88).[29] The bacteria are stable in the environment for 17 hours in sunlight, 46 hours on glass, less than 7 days on floors, 42 days in carcasses and organs, and 60 days in meat products.[35]

Geographical Occurrence

S. aureus is a major human pathogen that is found worldwide. It appears to have a predominantly human reservoir and can be isolated from the nares of about 30% of healthy adults.[36] MRSA has emerged in developing countries, where it remains common.[37] In some parts of the United States, the majority of community isolates of *S. aureus* from ill patients are now MRSA.[38]
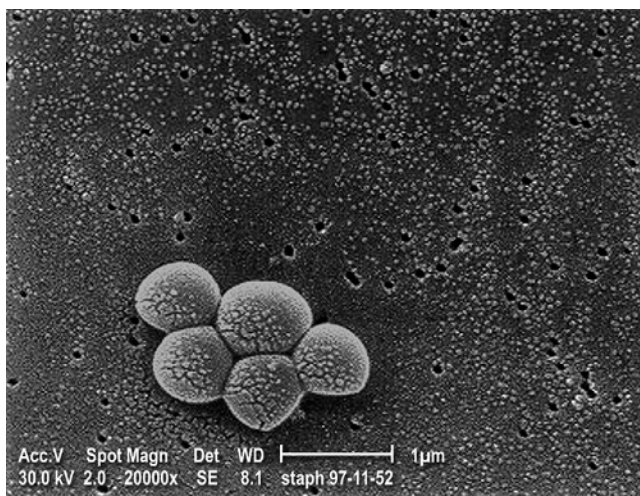
Figure 9-88 ▪ Magnified (×20,000), this scanning electron micrograph depicts a grouping of MRSA bacteria. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Photo Courtesy Janice Carr.)

Groups at Risk

The major risk factor for MRSA infection continues to be contact with the health care system, such as a recent hospitalization, nursing home stay, or surgery.[39] Studies of hospital personnel have found MRSA in nasal carriages in 6% of persons sampled.[1] For cases that arise in the community, reported risk factors include age younger than 2 years, low socioeconomic status, participation in contact sports, injection drug use, men who have sex with men, military personnel, inmates of correctional facilities, veterinarians, pet owners, and pig farmers.[40]

Hosts, Reservoir Species, Vectors

Although humans are considered the primary host for *S. aureus* infection, *S. aureus* is clearly a commensal of many other species. In addition to skin and soft tissue infection, pneumonia, and other pathologic conditions, asymptomatic nasal carriage rates of 30% or greater have been reported. Previous surveys have indicated that human nasal carriage rates of MRSA are much lower than for *S. aureus* in general, but this may be changing.[41]

In animals, *S. aureus* is not as common a pathogen as other *Staphylococcus* species such as *S. pseudintermedius* (previously referred to as *S. intermedius*).[7] However, recent studies have found significant carriage rates of MRSA in dogs and cats from almost all body sites tested (wounds, abscesses, and chronic pyodermas). Other animals that carry MRSA include horses, pigs, elephants, rabbits, cattle, and birds.[4,12,14-15,17,21,42,43] Strain-typed MRSA infections found in dogs and cats are typically indistinguishable from predominant human strains.[3,6,8,44,45] To date, studies have shown transmission of MRSA from people to animals and animals to people, but it is not clear whether animals are a significant reservoir for people. However, evidence suggests that several new MRSA strains may have entered human populations from pigs and cattle.[4] A study in a small animal hospital found 9% of the dogs were MRSA carriers, whereas almost 18% of the staff was infected.[5] Among *S. aureus* isolates from sick animals in veterinary teaching hospitals, 14% were MRSA.[46] Among healthy dogs and cats in the general population, MRSA prevalence has been reported at 1% to 3%, although there was a high rate of infection with methicillin-resistant coagulase-negative *Staphylococcus* (MRCoNS).[14] The epidemiology in pigs may be different. A relatively high prevalence of nasal carriage of MRSA has been reported[47] in agreement with previous studies showing transmission between pigs and farmers.[14]

MRSA infections associated with pigs and calves have emerged as a significant concern in Europe. Studies have identified pig or calf contact as significant risk factors for both colonization or infection with a specific MRSA strain, called ST398, which has been found in pigs in Europe, Asia, and North America.[15-17,42] Astoundingly high rates of colonization have been identified in pig and cattle farmers.[15,16,25] There is concern that this strain is now causing infections beyond direct human contacts and that farm animals may be an important reservoir of this strain for human infections.[25,48,49]

Mode of Transmission

The risk of transmission between humans and other animals may vary by species and type of MRSA (Figure 9-89). One study found evidence of MRSA transmission between dogs and veterinary workers.[50] Equine-human zoonotic transmission has been fairly clearly established.[12]

The mode of transmission in the community is thought to be primarily by hands that become contaminated by contact with colonized or infected body sites of other individuals or fomites contaminated with body fluids containing MRSA. Other factors contributing to transmission include skin-to-skin contact, crowded conditions, and poor hygiene.[51] Risk factors for acquisition of MRSA are likely to include certain antimicrobial use in veterinary medicine.

Environmental Risk Factors

MRSA can persist on environmental surfaces and has been cultured from surfaces in veterinary hospitals.[4] Despite finding MRSA on various environmental surfaces, evidence of surfaces as a source of infection is weak; direct contact with humans or animals is a much more likely route of transmission.
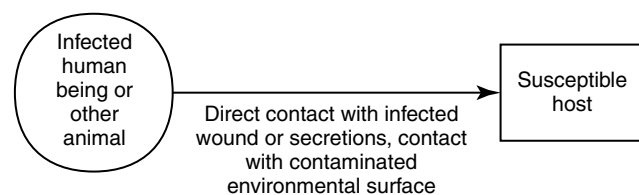

Figure 9-89 ▪ Life cycle, MRSA infection.

Disease in Humans

S. aureus typically causes skin and soft tissue infection, including furunculosis, folliculitis, and cellulitis. The more invasive strains of MRSA have been associated with necrotizing pneumonia and necrotizing fasciitis (Color Plate 9-45). Sepsis can occur with any strain. Often the first sign of infection is a small pustule or area of redness. This can rapidly progress to a localized abscess or a more generalized infection (Color Plate 9-46).

Disease in Animals

Infection in animals, while often subclinical, can be associated with a wide range of opportunistic infections, ranging from skin and soft tissue infections to pneumonia and sepsis (Color Plate 9-47). *S. aureus* causes mastitis in cows, and milk is a recognized source of *S. aureus* infection (but not MRSA). Surveys of dairy products have detected MRSA in milk and cheese.[52] Table 9-44 provides comparative clinical presentations in humans and other animals.

Diagnosis

In humans and animals, the cornerstone of diagnosis is culture with appropriate sensitivities. Genotyping can provide information about strain type but does not provide any guidance regarding clinical management. For rapid diagnosis in human patients, a Gram stain showing gram-positive cocci in clusters is suggestive of *S. aureus* infection. This does not apply in animals where other *Staphylococcus* organisms are common.

Some veterinary laboratories may not perform the studies necessary to identify a case of staphylococcal infection as *S. aureus* or MRSA because traditionally *S. pseudintermedius* has been a more important pathogen.

Treatment

Table 9-45 outlines treatment guidelines in humans and other animals. Since clindamycin resistance occurs in some cases, a test for inducible resistance "double D" (double disk diffusion)

Table 9-45 ■ MRSA Treatment in Humans and Other Animals		
Species	**Primary Treatment**	**Alternative**
Humans (health care–associated)	Vancomycin	Teicoplanin, daptomycin, linezolid, dalbavancin, TMP-SMX (test susceptibility first)
Human (community acquired): abscess, immunocompetent, afebrile (outpatient care)	TMP-SMX double strength	Doxycycline *or* minocycline *or* clindamycin
Abscess with fever (outpatient care)	TMP-SMX double strength ± rifampin	Clindamycin *or* doxycycline
Pneumonia	Vancomycin IV	Linezolid IV
Bacteremia, endocarditis, septic	Vancomycin IV	Daptomycin IV[53]
Dogs	Chloramphenicol 33 mg/kg tid	
Cats	Chloramphenicol 50 mg/kg bid	
Horses	Based on susceptibility testing	
Cattle	Based on susceptibility testing	

D-test, Double-disk diffusion; *quino/dalfo*, quinupristin/dalfopristin; *TMP-SMX*, trimethoprim-sulfamethoxazole.

or D-test should be performed before using this agent.[53] Antimicrobial therapy should be based on antibiogram as well as patient (e.g., age, renal function) and infection factors (e.g., location, organic debris, drug penetration). In most cases, MRSA isolates are susceptible to a variety of antimicrobials, and commonly used antimicrobials such as chloramphenicol may be used. Trimethoprim-sulfamethoxazole is often useful;

Table 9-44 ■ Methicillin-Resistant *Staphylococcus Aureus:* Comparative Clinical Presentations in Humans and Other Animals			
Species	**Risk Factors for all Species**	**Clinical Manifestations**	**Laboratory Findings**
Humans	Contact with a colonized or infected person or animal; nosocomial contact; poor hygiene	Soft tissue infection, pneumonia	Gram stain showing gram-positive cocci in clusters, culture and sensitivity, PFGE, spa typing, latex agglutination for PBP2a
Dogs		Soft tissue infection	
Cats		Soft tissue infection	
Horses		Soft tissue infection, joint infections, pleuropneumonia	
Cattle		Mastitis	
Pigs		Subclinical carriage, rare skin infections	

PBP2a, Penicillin-binding protein 2a; *PFGE*, pulsed-field gel electrophoresis.

however, adverse effects (keratoconjunctivitis sicca, arthropathy) must be considered. Aminoglycosides are often effective but must be administered parenterally. Some isolates may appear susceptible to fluoroquinolones in vitro, but this class of drugs should not be used because in vivo response is typically poor and resistance develops quickly.

There is currently controversy about the use of drugs in a veterinary setting that are important in human medicine (i.e., vancomycin, linezolid). Although veterinarians have the ability to use such drugs in an extra-label fashion, ethical issues about the use of these critically important human drugs should be considered, and if used, they should only be used in extreme circumstances when no other options exist and the infection cannot be treated topically or in some other manner.

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ORF

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Other orthopox infections (ICD-10 B08.0)

Other names in humans: ecthyma contagiosum, contagious ecthyma virus, contagious pustular dermatitis virus, contagious pustular stomatitis, giant orf

Other names in animals: cutaneous ecthyma, scabby mouth disease, sore mouth disease, ovine pustular dermatitis

Infection with orf virus is primarily a disease of sheep and goats that can significantly affect husbandry operations. Transmission of the disease to humans was first recognized in the 1930s[1-3] and remains an occupational risk to those who handle these animals, particularly immunocompromised individuals. It is also a hazard in public settings such as petting zoos and county fairs. Recent outbreaks in the United States have underscored the importance of differentiating orf virus infection from life-threatening or other rare diseases in humans and from other economically significant diseases in animals such as foot and mouth disease (FMD).

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide descriptive epidemiology for the community.
- Educate local veterinary and human health clinicians in risk areas and during high-risk periods about groups at risk and the signs and symptoms of disease.
- Educate the public, especially parents, on ways to prevent general transmission of infection on farms and petting zoos.
- Encourage handwashing after handling animals.
- Provide animal owners and exhibitors with the *Compendium of Measures to Prevent Disease Associated with Animals in Public Settings.*[4]
- Work with local agricultural authorities to exclude potentially infected animals from fairs, exhibitions, and other locations where cross-infection could occur.
- Encourage barrier protection such as the use of nonporous gloves when handling infected or recently vaccinated animals in addition to handwashing.
- Encourage animal owners and exhibitors to carefully monitor their animals and promptly quarantine those that present lesions or were recently vaccinated.[5]

Human Health Clinicians

- Consider the diagnosis in humans compared with other life-threatening conditions such as cutaneous anthrax.
- Counsel at-risk workers regarding the importance of protecting open wounds, using nonporous gloves, and handwashing when caring for infected or recently vaccinated sheep and goats[5-7] and to use caution when handling the animal vaccine.
- Counsel immunocompromised individuals or those with chronic skin disorders to avoid contact with potentially infected animals.
- No human vaccine is available.

Veterinary Clinicians

- Consider orf in the differential diagnosis of vesicular lesions, including foot and mouth disease.
- Counsel farmers to remove thistle and harsh brush from grazing areas, which can reduce skin trauma to the mouth and muzzle area necessary for transmission of the virus.[6]
- Counsel animal owners to refrain from bringing infected or recently vaccinated animals to public events or shows.
- Advise PPE and sharps injury prevention for veterinary staff and farm workers during vaccination and care of infected animals.
- Ensure that veterinarians and veterinary staff can recognize signs of occupational infection and seek care.
- Report disease to veterinary/agriculture and public health authorities as well as occupational health care providers caring for at-risk workers.
- Live, nonattenuated orf virus vaccines are commercially available.[5] Preparations can also be made from scabs of

previously infected animals. Both types are potentially infectious to humans who handle the vaccine, experience a sharps injury during vaccine administration, or have contact with the vaccine site or recently vaccinated animals.[5] Orf virus vaccines are intended to produce controlled infection in flocks and will ultimately seed the environment with virus-containing scabs.[6] Thus vaccination should be used only in previously infected flocks.[8,9] The immunity conferred by current vaccines is not lifelong and failures have been reported.[5] The 2001 USDA National Animal Health Monitoring System (NAHMS) sheep survey reported that 5% of sheep operations vaccinated replacement or breeding ewes and 14% vaccinated nursing lambs.[10] In counseling animal owners who are considering vaccinating their livestock, veterinary clinicians should:

- Encourage the vaccination of lambs at ≈1 month of age and a second vaccination at 2 to 3 months for at-risk lambs.[11]
- Provide proper precaution to prevent outbreaks and transmission to humans associated with vaccine use.
- Discourage the use of vaccines in flocks that have not previously been infected.

Agent

Orf is caused by *Parapoxvirus ovis*, also known as *orf virus* (Figure 9-90). It is a highly epitheliotropic poxvirus of the
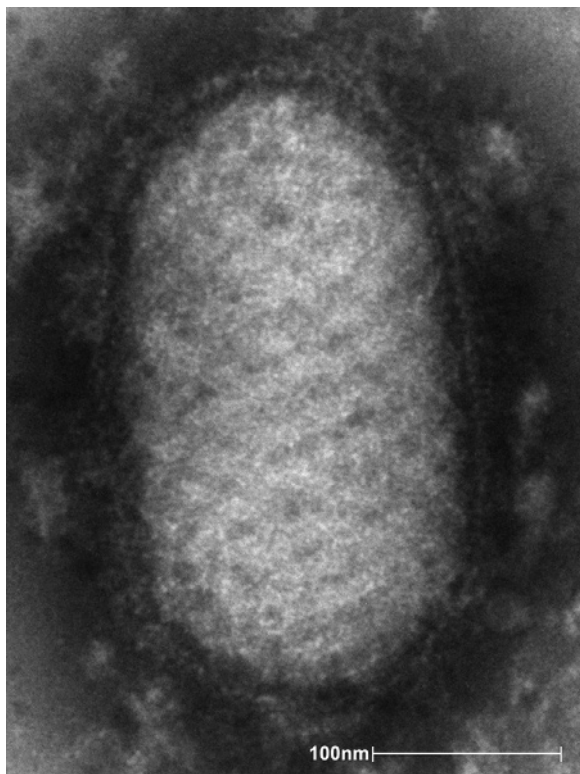
Figure 9-90 ▪ Negative-stained transmission electron micrograph image depicted the ultrastructural details of an orf virus, a member of the genus *Parapoxvirus*. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Photo courtesy A. Likos.)

family Poxviridae with a double-stranded DNA genome of approximately 140 kb.[12] It can be visualized by electron microscopy of negatively stained samples and appears as a cylinder of roughly 260 × 160 nm with a crisscross pattern characteristic of poxviruses.[7,13] Several other related parapox viruses cause zoonotic infections. Paravaccinia virus (also known as pseudo-cowpox) infect the teats of cattle and cause nodular lesions on the hands of dairy workers (milker's nodule).[12] Other zoonotic parapox virus infections include bovine papular stomatitis and seal pox.[14]

Geographical Occurrence

Orf virus is found worldwide with a higher prevalence in countries with extensive sheep and goat populations.[6-8] According to the 2001 national USDA NAHMS survey, 40% of U.S. sheep operations reported cases of orf infection within the past 3 years.[10] Human cases in recent years have been reported in Illinois, Tennessee, Missouri, New York, and California.[5,6] The incidence of human cases reflects the prevalence of infection in sheep and goat populations. However, cases in humans are probably underreported because those at risk are often familiar with the disease, recognize that it is self-limiting, and choose not to seek medical attention.[1,2,16,17] The fact that many laboratories lack the diagnostic capability for orf virus testing may further contribute to underreporting of the disease.[6]

Groups at Risk

Orf virus is an occupational risk to those who handle sheep and goats, including farmers, shepherds, veterinarians, butchers, and abattoir workers.[2,16] Wildlife researchers with contact with wild sheep and goat species are also at risk. These groups are especially at risk during the primary lambing season (spring and summer) because young animals are more susceptible to infection.[1,5,12] Those handling orf vaccines or recently vaccinated flocks are at greater risk of developing an infection.[1,5,6] Children may be at greater risk in both occupational (e.g., family farm) or recreational (e.g., petting zoo[4]) settings because common childhood behaviors such as nuzzling animals can lead to significant skin contact or bites.[5] Furthermore, children may be less likely to wash their hands or use gloves than adults.[5] Orf has been reported in conjunction with religious holidays during which families customarily slaughter a sheep or cow.[12,16,17] Contact with wildlife such as deer can also result in transmission to humans.[18] Patients with chronic skin disorders such as eczema are at increased risk for contracting orf infection.[5] Immunocompromised individuals are at risk for more severe disease.[6]

Hosts, Reservoir Species, Vectors

Small ruminants including sheep and goats are the predominant species affected, although infection has been reported in gazelles, musk oxen, alpacas, camels, deer, reindeer, and dogs.[7,19,20] Wild bighorn sheep (*Ovis canadensis*) and other wild sheep and goats can be infected. Certain breeds such as Boer goats are particularly susceptible to infection.[8,19] Humans are accidental hosts.
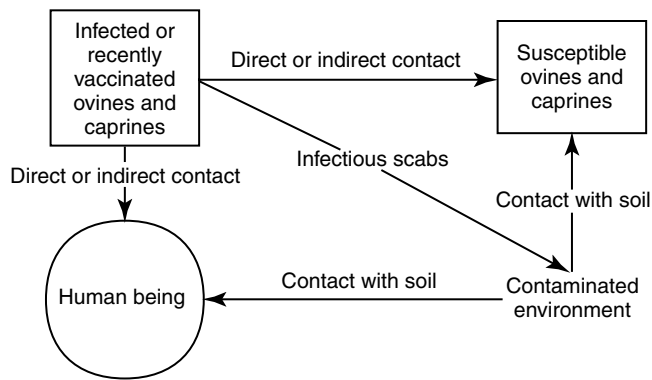
Figure 9-91 ■ Life cycle of orf virus.

Mode of Transmission and Life Cycle

Orf virus is transmitted via direct contact with broken skin or mucous membranes (Figure 9-91). Skin trauma is considered a predisposing factor in both animals[9,19,21] and humans.[5,6,9] Modes of transmission between animals include contact with infected animals or fomites such as bedding, feed, stalls fences, and trailers.[7,8] Because young animals are particularly susceptible due to their developing immune systems, outbreaks often occur during the principal lambing season.[1,5] Suckling can lead to lesions on the mother's teats and cause her to withhold feeding, leading to the spread of the disease to non-mother adults or to humans via tube- or bottle-feeding practices.[5]

Transmission from animals to humans can be facilitated by either minor (thistle pricks, torn cuticle) or severe (animal bite) skin trauma.[5,6] Other human activities that can lead to infection include shearing, petting, and handling infected equipment.[8] Orf virus can persist in wool and hides for over a month after the resolution of lesions, putting butchers, abattoir workers, and shearers at risk.[7,22] Orf virus vaccine is a live, nonattenuated preparation that has been known to cause outbreaks among sheep and human handlers.[6,7] Human-to-human transmission of orf infection has yet to be reported.

Environmental Risk Factors

Infected animals can shed virus-containing scabs that persist in animal housing and other inanimate objects such as harnesses, and pastures.[7,8,12] This environmental contamination can lead to indirect infection of other animals and humans. Although the virus is susceptible to ultraviolet rays, it is resistant to desiccation, temperature drops, and other environmental stressors and can survive in the soil and on surfaces for months.[7,13,22]

Disease in Humans

Initial signs of infection appear at the site of skin penetration after a 2- to 3-day incubation period. Lesions can reach 3 cm in diameter and typically occur on the hands or forearms, although infection of the face has also been reported.[2]

Symptoms of infection progress through several stages, each lasting approximately a week.[2]

The maculopapular stage begins with isolated or multiple erythematous macules and papules appearing at the site of contact that may be pruritic. The target stage features the development of vesiculonodules characterized by a white ring enclosing a red center (Color Plate 9-48). This is followed by an acute stage with an erythematous nodule with weeping, bleeding, and eventual crusting.

In immunocompetent patients, the infection is usually self-limited with full healing without scarring over a 6-week period.[5,6,13,16] Bacterial superinfection of the lesions may occur.[7,13] Other reported complications include pain, fever, malaise, erythema multiforme, blindness from ocular involvement, lymphangitis, and autoimmune pemphigus with bullous eruptions.[1,13,17,22-24] Immunocompromised patients are at greater risk for these complications, in addition to progressive or recurring "giant" lesions.[5,6,8,13] Infection with orf confers immunity, but reinfection has been reported, although it is typically less severe.[1]

Disease in Animals

Although animals of any age are susceptible, the disease is seen primary in animals younger than 1 year because adult animals are typically immune as a result of previous contact.[5] Outbreaks among livestock tend to occur in spring and summer.

Lesions occur primarily on the muzzle, nostrils, ears, lips, eyelids, lower legs, buccal mucosa, or teats, especially when nursing.[2] Boer goats may develop suppurative arthritis, chronic fibrinous pneumonia, and premature thymic involution.[19] No loss of appetite or difficulty in nursing was reported in lambs infected with buccal cavity lesions.[21] Recovery occurs within a month. Some animals may require feeding assistance. Animals can be infected more than once during their lifetime, but infections occur far apart and young animals present with the most severe cases.[8] Table 9-46 shows comparative clinical presentations in humans and other animals.

Diagnosis

Diagnosis in Humans

The diagnosis of orf in humans can be made clinically based on a history of exposure to sheep or goats and the presence of characteristic skin lesions. The differential diagnosis includes a number of potentially life-threatening infections, including cutaneous anthrax,[5] tularemia, and erysipeloid.[5,6] Other similar conditions include milker's nodule, cowpox, pyogenic granuloma, and skin cancer.[3,17] Clues to the clinical diagnosis include a history of exposure to sheep, goats, deer, and alpacas in petting zoos, farms, or other settings such as fairs, especially if animals were recently vaccinated or have skin lesions. Laboratory diagnostic techniques include PCR, electron microscopic histopathological analysis, and viral isolation, but these tests are not widely available.

Table 9-46 ▪ Orf Virus: Comparative Clinical Presentations in Humans and Other Animals				
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**	**Laboratory Findings**
Humans	Direct contact with infected animals; contact with soil and objects contaminated by animals, vaccine exposure	3-7 days	Maculopapular eruption progressing to weeping nodule	PCR, EM, viral isolation
Sheep, goats, alpaca, camels, deer	Contact with infected or recently vaccinated animals or contaminated environments	2-3 days	Papules, vesicles, pustules on the lips, mouth, nostrils, eyelids, ears, extremities	PCR, EM, viral isolation

EM, Electron microscopy; *PCR*, polymerase chain reaction.

Diagnosis in Animals

Lesions in animals can resemble foot and mouth disease because both diseases can present as erythematous, ulcerated papules.[6,9,21] The main clinical sign differentiating orf from foot and mouth disease is the proliferative nature of the lesions.[21] As with humans, the diagnosis can be confirmed with PCR or viral isolation.

Treatment

Orf infections in immunocompetent persons typically resolve spontaneously over 3 to 6 weeks.[2] Some treatments, including 40% topical idoxuridine,[2,5] imiquimod,[12] or cidofovir cream, accelerate the resolution of lesions.[24] Cleaning and antiseptically dressing the lesion can reduce the risk of secondary infection.[2] Surgical treatment may be used in severe cases but can occasionally result in the formation of satellite lesions.[2] The course of treatment usually depends on the location of the lesion.[13]

In animals, repellent should be applied to avoid development of myiasis caused by larvae from the fly *Cochliomyia hominivorax*.[7] Cases of bacterial superinfection can be treated with antibiotics.

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PLAGUE

Peter M. Rabinowitz and Lisa A. Conti

Plague (ICD-10 A20)

Other names in humans: bubonic plague, pneumonic plague, septicemic plague, black death

Other names in animals: feline plague, rodent plague, sylvatic plague

Yersinia pestis, the agent of plague in humans and other animals, has caused some of the largest epidemics in history. Plague continues to be an important and potentially fatal zoonotic disease, with 1 to 40 reported cases each year in the United States associated with rodent and flea contact and occasionally contact with sick cats.[1] Worldwide, several thousand cases are reported yearly to the World Health Organization. *Y. pestis* is a category A potential biological warfare agent. Despite its fearsome reputation and sensitivity to prompt antibiotic treatment, delays in diagnosis of plague in both humans and animals are frequent, often with tragic consequences. There is a continuing need for heightened awareness of the disease, especially in enzootic areas.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide descriptive epidemiology of the disease in the health district. Use of GIS risk mapping has been helpful in determining areas of high risk for endemic plague.[2]
- Educate the public about measures to reduce risk, including the following:
  o Control rodents and their fleas near dwellings (flea control should precede rodent control to prevent fleas from seeking new hosts); Box 9-5 lists steps for rodent-proofing homes.
  o Avoid camping near rodent burrows.
  o Avoid handling wild rodents (plague in the United States is strongly associated with ground-dwelling sciurid rodents, such as various species of prairie dogs and their fleas).
  o Use flea control on cats and dogs.
  o Prevent pets from hunting.[1]
- Conduct an immediate investigation of human, cat, or dog cases; consider the possibility of deliberate use (biological warfare).
- Ensure flea control in an outbreak situation before initiating rodent control measures.
- Ensure that persons with exposure to cases of pneumonic plague or other high-risk exposures (including exposures to cats with plague) are receiving antibiotic prophylaxis (see below) and are maintained under surveillance for 7 days.

BOX 9-5   *STEPS FOR RODENT-PROOFING HOMES*

- *Seal* rodent entry holes or gaps with steel wool, lath metal, or caulk.
- *Trap* rats and mice using appropriate snap trap.
- *Clean up* rodent food sources and nesting sites.
- Keep wood piles and compost heaps away from the house.
- Take precautions when cleaning rodent-infected areas:
  o Use cross-ventilation when entering a previously unventilated enclosed room or dwelling before to cleanup.
  o Use rubber, latex, vinyl, or nitrile gloves.
  o Do not stir up dust by vacuuming, sweeping, or any other means. Instead, thoroughly wet contaminated areas with a bleach solution or household disinfectant. *Hypochlorite (bleach) solution:* mix 1½ cups of household bleach in 1 gallon of water. Once everything is wet, take up contaminated materials with damp towel and then mop or sponge the area with bleach solution or household disinfectant.
  o Spray dead rodents with disinfectant and then double-bag along with all cleaning materials and dispose of bag in an appropriate waste disposal system.
  o Remove gloves and thoroughly wash hands with soap and water (or waterless alcohol-based hand rubs when soap is not available and hands are not visibly soiled).

- Ensure that workers with occupational risk for *Y. pestis* infection receive adequate surveillance and reduction of exposure risk through exposure controls and protective equipment.
- A plague vaccine is being developed.

Human Health Clinicians

- Consider the diagnosis in all patients with recent travel or residence in an enzootic area, with occupational exposure (such as veterinarians or wildlife workers), history of handling rodents, rabbits, or flea bites, as well as the possibility of deliberate use.
- Report disease immediately to public health authorities using the CDC case definition (see http://www.cdc.gov/ncphi/disss/nndss/casedef/plague_current.htm). CDC, Fort Collins, is a WHO Collaborating Center for Reference and Research on Plague Control, and reports all human plague cases in the United States to the WHO.
- Ensure patients are hospitalized with drainage and secretion precautions (bubonic plague) and maintain droplet precautions until 48 hours of appropriate antibiotic treatment has been completed with clinical improvement (including defervescence).
- Counsel patients in endemic areas with rodent exposure or with cats or dogs in risk reduction measures, including regular use of flea control (see above).

Veterinary Clinicians

- Consider the diagnosis in any sick cat from an enzootic area with fever, lymphadenopathy, and abscesses on the head and neck or progressive respiratory signs

accompanied by other systemic signs. The submandibular lymph node is the most common site of lymphadenopathy due to the inoculation of the oral mucosa from ingestion of plague-infected rodents.

- Train veterinary personnel in biosafety measures such as masks and gloves when working with potentially infected animals. N-95 respirators are recommended.[3]
- Treat animals at the veterinary hospital for 48 to 72 hours and observe clinical improvement (including defervescence) before allowing animal to be treated at home. This will ensure that owners will not be exposed to infectious saliva and other secretions when handling or treating their pet.
- Isolate and control fleas on suspected cases while treating with antibiotics.
- Follow local and state reporting regulations; contact local health department immediately regarding suspected animal cases.
- Recommend keeping cats indoors.
- Counsel clients not to let cats and dogs roam outside or otherwise come in contact with wildlife in endemic areas, and to treat monthly to control and prevent flea infestations.
- Store animal food in rodent-proof containers.
- A plague vaccine for use in endangered black-footed ferrets has been developed and used.[4]

Agent

Y. pestis is a gram-negative, bipolar staining, nonmotile bacillus that is a member of the family of Enterobacteriacae.[5] The CDC classifies *Y. pestis* to be a category A biological warfare agent due to its ability to be produced and disseminated in quantities sufficient to affect large populations and its high case fatality rate among untreated persons. It is believed that deliberate use of the agent would be in an aerosol form.[6]

Geographical Occurrence

Plague occurs in localized areas on most continents, with most cases being reported in less-industrialized countries (Color Plate 9-49). Some cases in developing countries are related to rats and their fleas in urban areas (urban plague). In the United States, most cases occur in rural areas west of the Mississippi, where the disease exists in wild (ground-dwelling) rodent reservoirs (sylvatic plague)—New Mexico, Idaho, Colorado, Nevada, Oregon, Texas, Arizona, California, Utah, Washington, and Wyoming. Mapping of rodent habitat in the Southwestern United States has successfully identified areas of increased human risk related to conifer forests and amount of precipitation. Much of the area of increased plague risk in the Southwest overlaps with risk areas for hantaviral infection, another rodent-borne disease.[7]

Groups at Risk

Groups at increased risk for *Y. pestis* infection include hunters, veterinarians, mammalogists, campers, hikers, Native Americans, owners of cats allowed to roam free, and rural residents in enzootic areas. A significant number of cat-associated human cases have occurred among veterinarians and veterinary assistants.[3,8] Most U.S. cases occur between May and October, when temperatures favor transmission from the fleas and potential human and rodent interactions are higher.[5]

Hosts, Reservoir Species, Vectors

Worldwide, an important reservoir for *Y. pestis* is domestic rats (*R. rattus and R. norvegicus*), especially in urban settings. In the United States, however, wild rodents are the principal reservoir species, including ground squirrels, rock squirrels, and prairie dogs.[9] In many of these species, susceptible individuals develop the disease and significant die-offs among colonies of some species of prairie dogs are well documented (Color Plate 9-50).[10] Black-footed ferrets, an endangered species, can become infected from preying on prairie dogs.[4] Risk of exposure to fleas infected by *Y. pestis* is elevated in areas adjacent to rodent colonies experiencing widespread mortality, and these die-offs provide a warning of infection risk to humans and domestic animals.

Fleas are the principal vector of plague. Urban plague has been linked to exposure to the oriental rat flea *Xenopsylla cheopis* (Color Plate 9-51), which commonly infests *Rattus* species. Fleas, once infected, may remain infectious for a year or longer.[11] Both male and female fleas can transmit the infection. Wild rodent fleas vary by species in their ability to be effective vectors. Cat fleas *(Ctenocephalides felis)* are considered poor vectors for plague.[3,11] The human flea (*Pulex irritans*) may spread the infection between humans in situations of crowding and poor sanitation.[11]

Mode of Transmission and Life Cycle

Plague is spread through flea bites, direct contact with an infected animal, and by inhalation of infectious aerosols (Figure 9-92).[12,13] Fleas that have ingested a blood meal from an infected host can then infect another animal through a bite.
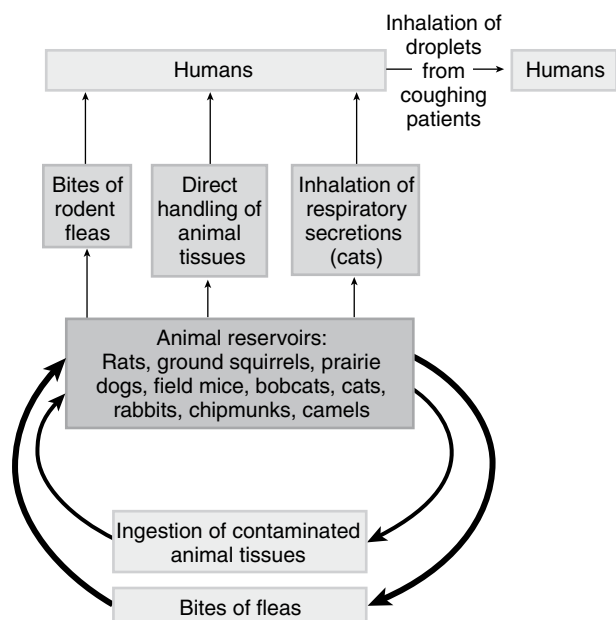

Figure 9-92 ■ Transmission of plague. The *wide arrows* indicate common modes of transmission, the *medium arrows* indicate occasional modes of transmission, and the *thin arrow* indicates a rare kind of transmission. (From Mandell GL (ed): *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone Elsevier.)

The usual source of human infection is a bite from an infected flea or direct handling of an infected animal carcass. Dogs and cats may bring fleas into a home where they can bite humans. Infected cats with pneumonic plague are a source of respiratory spread to humans. Person-to-person transmission through infectious aerosols occurs when there is respiratory involvement but has not been documented in the United States since 1924.

Environmental Risk Factors

The bacterium does not appear to survive long outside a mammal host. It can be destroyed by sunlight and drying.[14] Environmental factors influencing the risk of plague include those driving increases in rodent populations. Human habitation encroachment into wildlife habitat is an environmental driver of infection risk, because it leads to contact between wild rodent reservoirs of the infection and their fleas and peridomestic rodents. Dogs and cats may contribute to this wildlife-human contact by bringing fleas into dwellings.

Disease in Humans

There are several forms of human plague infection:
- *Bubonic plague* usually results from a flea bite or direct contact with an infected animal. There can be a local reaction at the site of the bite. After 2 to 6 days, fever, weakness, and malaise develop with lymphadenopathy. The swollen, extremely tender lymph nodes (buboes) typically occur most commonly in the groin, neck (rarely), or axilla and are often unilateral (Color Plate 9-52). Bacteremia is common. Without treatment, bubonic plague can progress to sepsis, shock, and death.
- Primary *septicemic plague* may develop without buboes. This form has a higher fatality rate than bubonic plague, possibly because of delays in diagnosis. Hypotension and disseminated intravascular coagulation can occur with shock and organ failure (Color Plate 9-53).
- *Pneumonic plague* may result from secondary spread to the lungs of bubonic plague or from primary infection caused by contact with a human or cat with respiratory involvement. Most cases of primary pneumonic plague in the United States are currently related to exposure to infected cats.[8] Pneumonic plague is highly fatal and can lead to further horizontal transmission to close contacts through respiratory spread.
- *Pharyngeal plague* also results from respiratory infection and is characterized by sore throat, pharyngitis, and local lymphadenopathy.
- Meningeal plague is rare but may be a complication of bubonic plague.[5]

Disease in Animals

Although certain subpopulations of the rodent hosts of the disease are apparently resistant to developing clinical infection, other individuals are susceptible, so that high mortality rates can occur. In these latter groups, such as prairie dogs, monitoring acute mortality can help predict plague activity in an area.

Cats are known to be susceptible to plague and can exhibit bubonic, pneumonic, or septicemic forms of the disease. Bubonic plague of the head and neck is the most common form in cats following bites from infected flea or consumption of infected rodents (Color Plate 9-54).[15] Secondary septicemic or pneumonic plague can also develop in cats; this form has led to primary pneumonic plague infection of humans in close contact with such cats (Figure 9-93). Signs in cats include fever, malaise, cough, and buboes. Without treatment, feline plague can be fatal in a substantial proportion of cases. Wild felids such as bobcats and mountain lions are also susceptible to plague.

Although dogs are less likely to develop clinical illness than cats, signs of infection have been documented in three naturally infected dogs in New Mexico (Color Plate 9-55).[16] Clinical signs included fever, lethargy, submandibular lymphadenitis, a purulent intermandibular lesion, oral cavity lesions, and cough. In dogs, antibodies to plague appear by day 8, peak by day 21, and decline by day 100 after exposure. This characteristic, combined with their relative resistance to clinical illness, makes dogs potentially useful as sentinels for plague risk in enzootic areas.

Table 9-47 summarizes the clinical presentations of plague in humans and other animals.

Diagnosis

The differential diagnosis of bubonic plague in humans includes other causes of acute lymphadenopathy, including bartonellosis (cat-scratch disease), staphylococcal abscess, tuberculosis, and lymphogranuloma venereum. The rapid onset and associated symptoms should help the clinician make the diagnosis. Pneumonic plague can resemble other rapidly progressive pneumonias. A history of exposure to fleas, rodents, sick cats, or wild carnivores can be helpful, as well as any information of recent outbreaks among animals or humans where the person lives or has recently traveled.

Samples of blood and wound drainage should be sent for culture and chest x-rays films should be obtained. A national network of laboratories has been established for rapid
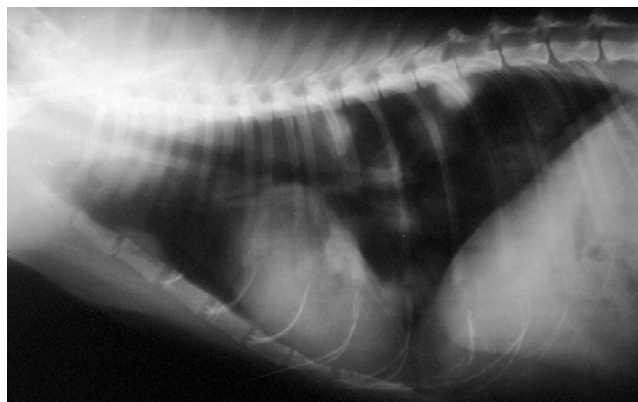

Figure 9-93 ■ Thoracic radiograph of a cat with pneumonic plague. (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy Dennis Macy, Colorado State University, Fort Collins.)

Table 9-47 ■ Plague: Comparative Clinical Presentations in Humans and Other Animals				
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**	**Laboratory Findings**
Humans				
Bubonic plague	Flea bite, contact with infected animal	2-7 days	Fever, lymphadenopathy	Elevated WBC count, abnormal liver function tests, culture of blood, DFA of LN aspirate
Septicemic plague			Fever, hypotension, DIC	
Pneumonic plague	Infectious aerosol	1-4 days[1]	Cough, hemoptysis, fever	Abnormal coagulation studies
Pharyngeal plague			Sore throat, pharyngitis, cervical lymphadenopathy	Pulmonary infiltrates on x-ray
Plague meningitis	Can result from bubonic plague		Meningeal signs	WBCs in CSF
Cats				
Bubonic plague (pneumonia may accompany)	Flea bites, ingestion of rodent	2-7 days	Lymphadenopathy with cellulitis on head and neck, abscess formation, drainage, fever, depression, dehydration, anorexia, oral ulcers	Culture of blood, lymph node biopsy or aspirate, DFA of LN aspirate Serology HI (may persist more than a year in surviving animals)
Septicemic plague			Fever, depression, vomiting	
Pneumonic plague	Inhalation of infectious aerosol		Fever, cough, bloody sputum[3]	
Dogs	Flea bites	7-10 days[17]	Often subclinical, mild fever, depression	Serology HI
Rodents, Rabbits	Flea bites	Days	May be subclinical in a minority of cases Death	

CSF, Cerebrospinal fluid; *DIC*, disseminated intravascular coagulation; *DFA*, direct immunofluorescence antibody; *HI*, hemagglutination inhibition; *LN*, lymph node; *WBC*, white blood cell.

diagnosis of plague, and consultation should be obtained regarding the appropriate testing facility to process specimens. In bubonic plague, the bubo can be aspirated and sent for Gram stain, Wayson stain, DFA, and culture.[5] PCR tests may be available. Diagnosis can be confirmed by serology obtained acutely and after several weeks showing a fourfold rise in titer, a single titer greater than 1:128,[18] or by positive bacteriophage testing from a culture isolate.

In animals, culture and DFA of tissues antibody serology testing are the mainstays of diagnosis. Diagnostic samples can include wound drainage, lymph node aspirates, blood, and necropsy specimens biopsy of liver, lung, spleen, or bone marrow. If there is evidence of respiratory involvement, a pharyngeal swab can be performed. Specimens should be kept chilled.[3]

Treatment

Treatment in Humans

Treatment in human beings with antibiotics should be begun as soon as the diagnosis is suspected. Patients should be hospitalized in an intensive care unit with wound drainage and droplet precautions until 48 hours of appropriate antibiotics with clinical improvement (including defervescence). Although streptomycin has the greatest proven efficacy, it is not widely available in the United States, and gentamicin or doxycycline may be used (Table 9-48).[19] If buboes become large and fluctuant they may require incision and drainage. Supportive care with intravenous fluids and close hemodynamic monitoring is necessary for most patients.

Persons with close contact with a patient or animal with pneumonic plague or other potential exposures (bite from a cat with potentially infectious saliva, bubo drainage in an open wound, and so on) should receive antibiotic prophylaxis and surveillance for symptoms for 7 days after exposure ceases.

Treatment in Animals

Infected cats should be hospitalized, isolated, and have immediate flea treatment with imidacloprid or pyrethrin. Antibiotics should be begun immediately and intravenous fluids and other supportive measures used aggressively. Cats with the pneumonic form of the disease should be considered for euthanasia if adequate infection control is not available in a veterinary hospital because of the infectious nature of the respiratory droplets and the high fatality rate of primary pneumonic plague.[17] Table 9-48 lists recommendations for antibiotic treatment of plague in humans and animals.

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Table 9-48 ■ Treatment of Plague Infection in Humans and Other Animals		
Species	**Primary Treatment**	**Alternative Treatment**
Humans (adult)	Gentamicin 5 mg/kg IV q24h *or* streptomycin 15 mg/kg gm IV bid	Doxycycline 200 mg × 1, then 100 mg PO *or* IV *or* ciprofloxacin 500 mg PO bid, *or* 400 mg IV q12h, *or* gentamicin plus doxycycline
Prophylaxis (close contact with infected animal or human)	Doxycycline 100 mg PO bid × 7 days[20]	Ciprofloxacin 500 mg PO bid × 7 days[20]
Cats	Immediate flea treatment Imidacloprid	
Bubonic form	Tetracycline 25 mg/kg PO q8h × 10 days; parenteral 7.5 mg/kg q12h Chloramphenicol 30-50 mg/kg PO q8h[21]	Doxycycline
Pneumonic form	Euthanasia if infection control is inadequate	
Dogs	Flea treatment Antibiotic treatment generally not necessary	

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Q FEVER

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Q fever (ICD-10 A78)

Other names in humans: query fever, coxiellosis, abattoir fever, Australian Q fever, nine-mile fever, quadrilateral fever, Balkan influenza[1]

Other names in animals: coxiellosis

Q fever is a disease caused by *Coxiella burnetii* that has a reservoir in a number of animal species. It is spread to humans by direct contact, most commonly through inhalation of organisms but also possibly through ingestion or other intake routes. It causes potentially serious disease in a proportion of people infected, and because of its high infectiveness and environmental persistence has been considered a potential bioterrorism agent. The true impact of Q fever as a zoonotic disease is probably underrecognized because of the nonspecific nature of the illness in many cases.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Human disease is reportable to public health authorities.
- In the event of a case report, determine whether others are at risk and whether there is an ongoing risk of exposure (consider bioterrorism potential of this agent).

- Recommend cleaning sources of contaminated soils and dusts from the environment (understanding that the organism is highly resistant to chemical and physical agents) and disinfection with 0.05% hypochlorite, 5% peroxide, or 1:100 Lysol solution.[2]
- Educate the public, veterinarians, and human health clinicians about risk factors for transmission; organisms localize in reproductive and mammary tissues and can be also be shed in urine and feces and spread by ticks (viable organisms have been recovered from tick feces after 19 months and after 42 months in milk at 4° to 6°C).[2]
- Support the maintenance of milk pasteurization to prevent infection in the general population.

Human Health Clinicians

- Report human disease to public health authorities. http://www.cdc.gov/ncphi/disss/nndss/casedef/q_fever_2008.htm.
- Consider diagnosis in high-risk individuals such as persons with occupational exposure.
- Consider in the differential diagnosis of patients presenting with culture-negative endocarditis.
- Provide occupational preventive services to high-risk individuals, including counseling on PPE and biosafety, as well as consideration of vaccine. Persons with valvular heart disease should not work in laboratory settings with *C. burnetii*.
- Vaccine: a vaccine has been developed for high-risk individuals in Australia but is limited to those at high risk of exposure and who have no demonstrated sensitivity to Q fever antigen.[3] The vaccine is not currently available in the United States either commercially or through an investigational new drug permit.
- Person-to-person transmission is rare but has been reported through sexual contact and to health care staff during obstetrical procedures on infected patients.

Veterinary Clinicians

- Instruct owners and any others in contact with infected animals to immediately seek medical advice.
- Segregate parturient animals and destroy (burn or bury) placentas and other reproductive discharges to reduce transmission.
- Ensure veterinary staff follow proper biosafety procedures, including around parturient animals.
- Isolate infected animals and implement airborne transmission precautions for staff.
- Ensure that ruminants used for research purposes are free of *C. burnetii* through serological testing.
- A vaccine for livestock has been developed and shown to reduce infection in calves and reduce shedding in previously infected animals. However, the vaccine is not currently commercially available in the United States.

Agent

Q fever is caused by *Coxiella burnetii*, a gram-negative obligate intracellular, coccobacillus organism in the gamma subdivision of Protobacteria (along with *Legionella*,
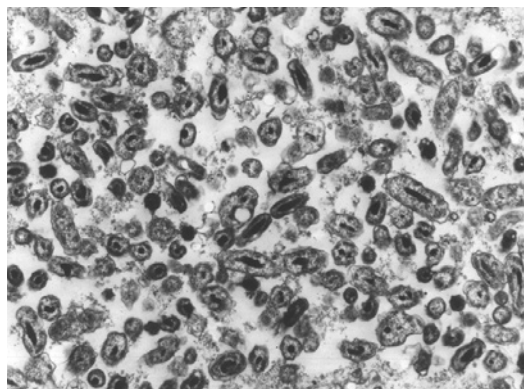

Figure 9-94 ■ Electron photomicrograph of *Coxiella burnetii*–infected caprine placenta. (From Songer JG, Post KW: *Veterinary microbiology: bacterial and fungal agents of animal disease*, St Louis, 2005, Saunders Elsevier. Courtesy Raymond E. Reed.)

Francisella, and *Rickettsiella*) (Figure 9-94). The organism is highly infectious, with an infective dose of 1 to 10 organisms.[3] It exists in two different antigenic phases, and the human antibody response generated to each antigen phase can be used to assess progression of infection. Phase II antibodies are more predominant in humans experiencing acute infection, whereas phase I antibodies are proportionately more common in chronic disease states, such as endocarditis.[4] There are also at least two different morphologic forms of the bacteria; one is large and bacilliform, another is small and coccoid. The small, high-density form (small cell variant [SCV]) has some resemblance to a spore in terms of its hardiness; it is highly resistant to environmental degradation and therefore plays an important role in transmission.

Geographical Occurrence

C. burnetii occurs worldwide. It is probably more prevalent than recognized owing to the often subclinical nature of disease in humans and animals and the difficulty with laboratory diagnosis. In 2000, cases were reported in California, Colorado, Idaho, Kansas, Minnesota, Nebraska, Nevada, Oregon, and Utah.

Groups at Risk

Q fever often occurs as an occupational disease. Workers at risk include slaughterhouse workers; veterinarians and veterinary staff; farmers; researchers working with pregnant animals, especially sheep; and workers in diagnostic laboratories where the organism may be cultured. However, even casual contact with farm environments or farm animals can lead to infection. Also, because the agent may be spread on dust, persons living near high-risk areas may be at risk for infection through windborne spread.

Although it is less commonly reported among children than adults, Q fever does occur in children, especially among those exposed to farm animals and farm environments for even brief amounts of time.[5] Children can also be infected by drinking raw milk, although they are typically asymptomatic.

Exposure to parturient cats has caused outbreaks in humans in the past among pet owners and their families.[6]

Hosts, Reservoir Species, Vectors

Animals are the natural reservoir for *C. burnetii*. It is found worldwide in sheep (Figure 9-95), cattle, goats, birds, dogs, and cats. Serological evidence of past exposure has also been shown in a variety of wild mammals. In the United States, seroprevalence studies have shown antibodies in more than 40% of sheep, 16% of goats, and 3% of cattle.[7] A study in Colorado found that more than 8% of female cats studied had evidence of *C. burnetii* in uterine tissue, raising the issue of risk to owners during birthing. A study in Asian cats found seroprevalence rates of up to 41% in stray cats and 14% in pet cats.[8] However, the risk of pet-to-human transmission may be low, as an Austrian seroprevalence study did not find that pet ownership was a risk factor for seropositivity to *C. burnetii*.[9]

Mode of Transmission and Life Cycle

Animals infected with *C. burnetii* shed high concentrations of the organism in birth products and milk, as well as lower concentrations in feces and urine (Figure 9-96). The organism can be tickborne in animal-to-animal transmission, but transmission from animals to humans is thought to result mostly from inhalation of droplets and/or aerosols containing organisms from infected placental tissue, other parturient tissues, and dusts containing dried body fluids. The organism is found commonly in raw milk with reported prevalence of >94%.[10] Milk pasteurization has been designed specifically to destroy this heat-resistant organism. Foodborne transmission to humans may occur rarely through unpasteurized milk. Transmission in domestic animals is thought, as in humans, to occur mostly through inhalation of infectious aerosols or ingestion of contaminated tissue.

Figure 9-96 ■ Life cycle, Q fever infection.
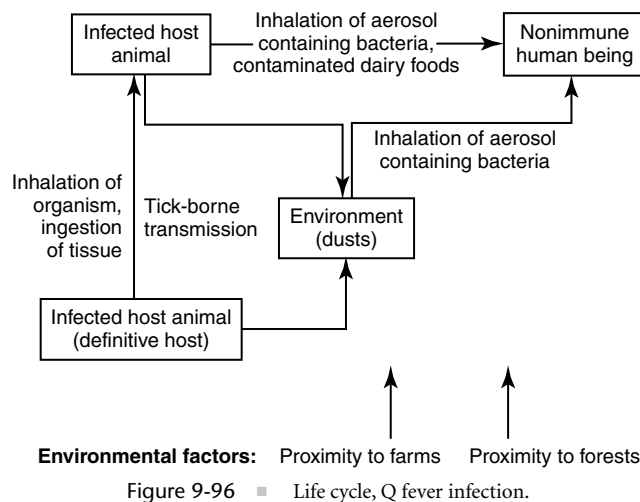
The agent can be found in a number of species of ticks, but tickborne transmission is believed to be more important in wildlife populations than in domestic animal or human infection.[1] However, the patterns of *C. burnetii* infection in wildlife remain poorly understood.

Environmental Risk Factors

Coxiella can persist for months in the environment. The SCV form of the bacteria that is shed in feces and other body fluids is similar in some ways to a spore and quite resistant to disinfectants and temperature extremes. Therefore infectious particles can persist in fomites and dusts, and aerosol transmission has occurred over long distances through windborne spread.[1] Proximity to farms is a risk factor for infection, as wind patterns appear to play a role in environmental transmission by dispersing infectious aerosols over wide areas.[11] Although the role of wildlife is not well understood, living near forested areas has been found to be a risk factor for suburban dwellers.[12]

Figure 9-95 ■ Infected sheep have been associated with outbreaks of Q fever in humans. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Edwin P. Ewing, Jr.)

Table 9-49 ▪ Q Fever Infection: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans	High-risk occupation	2-3 weeks (acute form)	Fever, malaise, chills, sweats, headache; hepatomegaly, abortion, placentitis	Serology, stained tissue (blood culture from endocarditis patients typically negative)
	Elderly, debilitated, underlying valvular disease	Months to years (chronic infection)	Chest pain	
Dogs	Tick exposure, contact with farm animals		Fever, neurological syndrome with vasculitis, including lethargy, anorexia, ataxia, seizures	PCR in some laboratories, serology (ELISA), and complement fixation
Cats	Tick exposure, contact with farm animals		Anorexia, lethargy, fever, abortion	
Cattle, sheep, goats	Inhalation of infectious aerosols		Anorexia, abortion	

ELISA, Enzyme-linked immunosorbent assay; *PCR*, polymerase chain reaction.

Disease in Humans

Q fever can present with acute or chronic symptoms (Table 9-49). Some cases in humans are asymptomatic or consist of sufficiently nonspecific symptoms, which results in missed diagnoses. After an incubation period of several weeks, the disease in its acute form often presents with fever, malaise, chills, weakness, headache, and sweats. Pneumonia is a predominant feature, although pulmonary symptoms may be absent even though pneumonitis may be seen on radiographs (Figure 9-97).[4] Chronic symptoms may develop over months to years. Chronic infection may include granulomatous hepatitis, meningitis, and osteomyelitis. The most serious form of chronic infection is bacterial endocarditis, which occurs particularly in persons with underlying valvular disease (Color Plate 9-56). Infection in children can often be asymptomatic but can also present acutely, with encephalitis and neurological symptoms.[13] In convalescent individuals, a postinfectious fatigue syndrome (fever fatigue syndrome) has been described.[4]

Disease in Animals

Animals typically do not manifest clinical signs with the exception of reproductive disease, especially abortion, infertility, and retained placenta (see Table 9-49; Color Plate 9-57). Because infection often goes unrecognized in animals human illness may serve as sentinel events, indicating the presence of infection in a domestic animal population.[14]

Diagnosis

The diagnosis in humans is usually made by serology. A rise in titers is seen in acute infection. Because the prevalence of antibody positivity in certain populations is relatively high, it is necessary to examine paired serological titers. Laboratories interpreting serological results need to use caution; misdiagnosis has resulted from improper interpretation.[15] IgM levels

greater than 1:128 suggest acute infection.[11] A PCR test has been developed to aid in diagnosis.[14] In chronic infection, high levels of phase I antibody titers (IgG >1:800) are seen, and phase I antibody titers are usually greater than phase II titers. Blood cultures appear sterile because of the need for intracellular cultivation. Although cell culture and embryonated egg methods exist to culture the organism from blood, laboratory workers are at risk of infection through such procedures, which should not be attempted outside a specialized laboratory experienced in handling the *C. burnetii* organism. The CDC can provide assistance in isolation. *C. burnetii* is considered a "select agent," so handling of live organisms in a laboratory setting is restricted. On biopsy tissue, immunostains and electron microscopy can be diagnostic for the *C. burnetii* organism.[4]

Serological testing is also used in animals. A fourfold increase in IgG over a 4-week period is diagnostic.[16] Tissue (aborted fetus, placenta) can be submitted for immunohistochemical testing. The organism can be isolated from blood in specialized test laboratories (New Mexico Department of Agriculture, Veterinary Diagnostic Services).[16]

Treatment

Acute Q fever is treated with doxycycline as a first-line agent. Chronic infection, including infective endocarditis in humans resulting from Q fever, is treated with a combination of antibiotics for an extended time (18 months to 3 years).

Although information on the efficacy of treatment in animals is limited, prophylactic treatment of endemic herds (or asymptomatic pets) with tetracyclines may reduce the zoonotic potential (rather than eliminate infection).[17] Other control measures include segregating pregnant animals indoors and burying or burning infected reproductive tissue wastes.[7] Table 9-50 provides antibiotic treatment information for Q fever infection in humans and other animals.
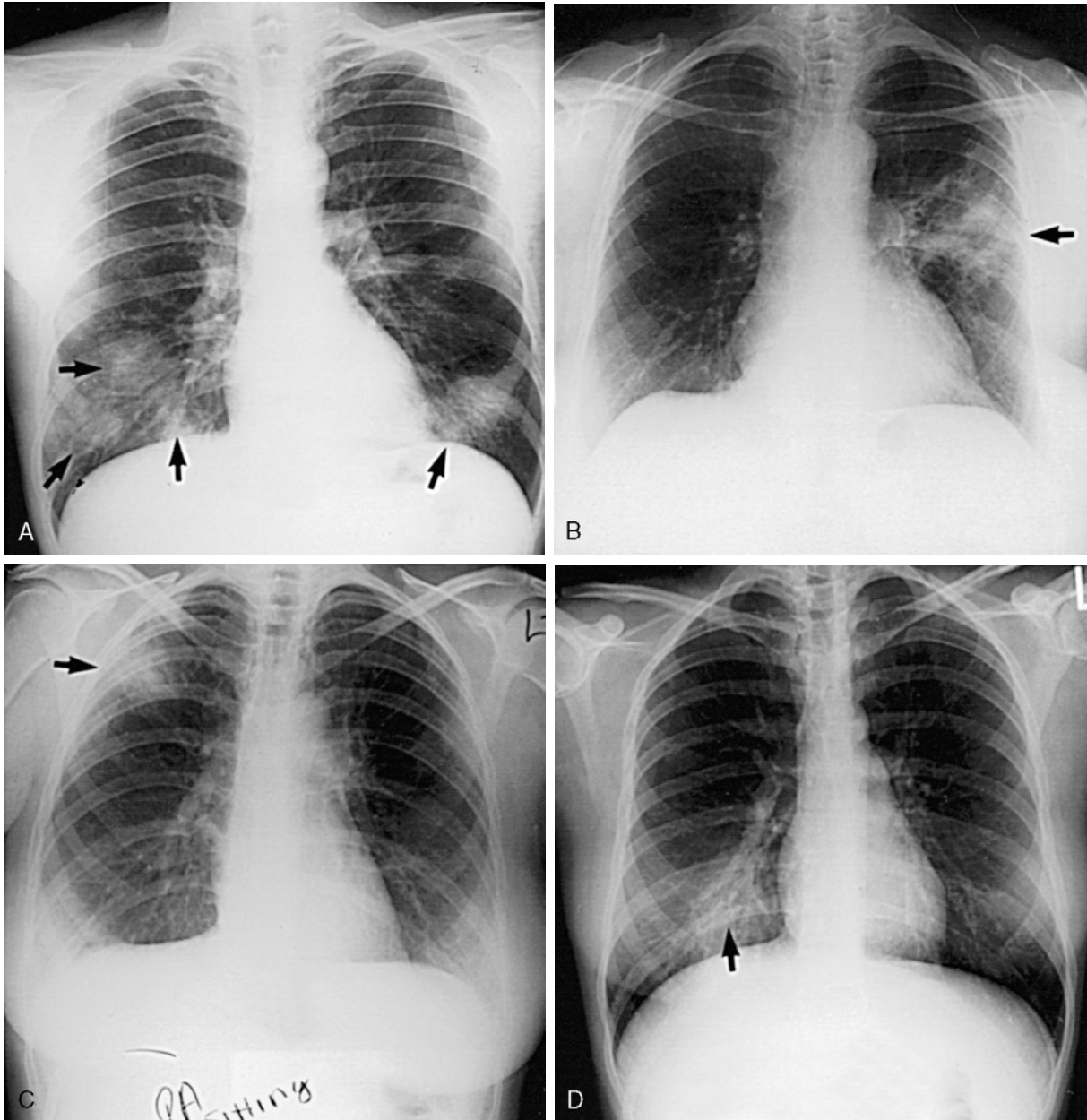
Figure 9-97 ■ Radiographic manifestations of Q fever pneumonia. All four patients are members of one family who developed Q fever after exposure to the infected products of feline conception. Their cat gave birth to kittens in their house. **A,** Multiple rounded opacities. **B,** Left upper lobe opacity. **C,** Pleural-based opacity involving the right upper lobe. **D,** Right lower lobe opacity. In an endemic area **A** is characteristic of cat-related Q fever pneumonia, and **C** is suggestive of this diagnosis. However, **B** and **D** are not at all distinctive and could be due to any pulmonary pathogen. (From Mandell GL, Bennett JE, Dolin R [eds]: *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2005, Churchill Livingstone Elsevier.)

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Table 9-50 ▪ Antibiotic Treatment of Q Fever Infection in Humans and Other Animals		
Species	**Primary Treatment**	**Alternative Treatment**
Humans: acute disease	Doxycycline 100 mg bid	Erythromycin
Chronic disease	Ciprofloxacin *or* doxycycline *PLUS* rifampin	Fluoroquinolone *PLUS* doxycycline × 3 yr
Endocarditis	Doxycycline 100 mg PO bid *PLUS* hydroxychloroquine 600 mg qd × 1-3 yr[18]	Pregnancy: need long-term TMP-SMX[18]
Acute disease	Doxycycline	Erythromycin
Chronic disease	Ciprofloxacin or doxycycline	Fluoroquinolone *PLUS* Doxycycline × 3 yr
Dogs	Tetracycline 22 mg/kg PO q8h × 2-6 wk	Doxycycline 20 mg/ kg PO q12h × 1wk
		Enrofloxacin 10 mg/kg PO q12h × 1 wk[16]
Cats	Tetracycline 10–20 mg/kg PO q8-12h × 2-3 wk	Doxycycline 5-10 mg/kg PO q12-24h × 2-4 wk
Cattle, sheep, goats	Tetracycline[7]	

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RABIES

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Rabies (ICD-10 A82)

Other names in humans: lyssa, hydrophobia

Other names in animals: rage

Rabies is one of the most feared zoonotic diseases because it almost invariably causes fatal human encephalitis. Despite the availability of an effective vaccine for humans and domestic animals, rabies continues to be a global public health problem. The first World Rabies Day by the Alliance for Rabies Control took place in September 2007, drawing attention to the need for human health and animal health professionals to work together to reduce this disease threat.[1] This is intended to be an annual event.

Human rabies is relatively rare in North America, but exposure to potentially rabid wild or feral animals occurs frequently. Owner noncompliance with rabies vaccination protocols of their pets, especially cats, can be a source of exposure as well. Managing and preventing such exposures requires an understanding by human health and animal health professionals of the status of rabies infection in local wildlife and domestic animal populations, the judicious use of vaccination strategies, and animal control measures.

Rabies can therefore serve as a model for improved communication and cooperation among public health, animal health, and human health professionals.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide rabies control and prevention guidance to the public, veterinarians, and human health clinicians (see World Rabies Day education bank, http://www.worldrabiesday.org/EN/Education-Bank/english.html). Risk reduction measures include:
  - Animal bite avoidance, especially with children
  - Keeping cats indoors and monitoring dogs when outside
  - Avoidance of feeding or handling wildlife or unknown cats and dogs
  - Appropriate exclusion of bats from buildings
- Analyze and report trends from compulsory reports of animal and human rabies.
- Advise the public that any bite wound or potential exposure to rabies should be thoroughly washed with soap and water, and the bite reported to local health authorities.

- Work with local human and veterinary medical providers and animals control officials in the management of potential rabies exposures.
- Support the preexposure vaccination of high-risk individuals.
- Explore methods of control of viral transmission in wildlife population (such as oral vaccine).
- Discourage ownership of pet wildlife or wild/domestic hybrids.
- Support appropriate vaccination requirements and policies to reduce translocation and importation of potentially rabid animals.
- Support scientific research on which to base public health policy.
- Provide access to appropriately trained laboratorians to diagnose the disease.

Human Health Clinicians

- In evaluating any patient with an animal bite, take an accurate history of the species involved and circumstances of the bite incident (see Figure 9-105).
- Coordinate with public health and animal control authorities as PEP may not be required if the animal is able to be tested, or the dog, cat, or ferret is available for observation. Certain monkey bites may need to be evaluated for herpes B exposure potential.
- Prevention of the development of clinical disease through the use of preexposure and postexposure vaccination strategies is the mainstay of preventing rabies deaths in humans. Become familiar with *Human Rabies Prevention—United States, 2008: Recommendations of the Advisory Committee on Immunization Practices (ACIP)* (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e507a1.htm). Ensure that candidates for PEP are rapidly evaluated and treated appropriately. Note that persons previously vaccinated with the human diploid cell vaccine (HDCV) or purified chick embryo cell (PCEC) vaccine should not receive human rabies immunoglobulin (HRIG).
- Report bite incident or use of PEP if required in the state.
- Report suspected human cases of rabies to public health authorities (consider using the Wisconsin protocol for rabies treatment: http://www.mcw.edu/FileLibrary/Groups/Pediatrics/InfectiousDiseases/Milwaukee_rabies_protocol2_1.pdf).
- Coordinate with state health authorities for collection of proper human diagnostic samples for rabies testing at CDC laboratories (http://www.cdc.gov/rabies/statehealthdept.html).
- Provide preexposure vaccinations to high-risk workers including veterinarians and staff working with rabies vector species and laboratory workers in facilities handling rabies vaccine. For persons previously unvaccinated against rabies, initial preexposure vaccination consists of a regimen of three 1-mL doses of HDCV or PCEC vaccines administered intramuscularly.
- Counsel travelers to rabies-endemic countries about the risk from exposure to dogs and other animals. Consider pretravel rabies immunization. In evaluating travelers returning from rabies-endemic countries, obtain history of any animal exposures (see Chapter 10).

Veterinary Clinicians

- Be familiar with the most recent National Association of State Public Health Veterinarians *Compendium on Animal Rabies Prevention and Control* (http://www.nasphv.org/Documents/RabiesCompendium.pdf).
- Ensure dogs, cats, ferrets, and appropriate livestock (e.g., horses) are currently vaccinated against rabies following the label use of the vaccine.[2] There is no parenteral vaccine approved for use in wolf hybrids or pet wildlife.
- Report adverse vaccine reactions, including rabies in a vaccinated animal to the USDA, APHIS, Center for Veterinary Biologics at http://www.aphis.usda.gov/animal_health/vet_biologics/vb_adverse_event.shtml.
- Work with public health officials in observing a healthy dog, cat, or ferret that has bitten a human for signs of illness within 10 days from the time of a bite. If no illness occurs, the person has not been exposed to rabies from that animal.
- Consider assisting public health officials by providing appropriate animal isolation and observation for clinical sign of rabies:
  - If a currently vaccinated dog, cat, or ferret is exposed to a known or suspect rabid animal, it should be revaccinated, confined, and observed for 45 days.
  - If the dog, cat, or ferret is not currently vaccinated, it should be isolated and observed for clinical signs of rabies for 6 months (vaccinated 1 month before release).
- Consider assisting public health officials by providing animal decapitation services for rabies testing.
- Consider rabies in the differential diagnosis of any dog, cat, ferret, horse, or livestock with behavioral changes or exhibiting unexplained neurological signs.
- Contact public health authorities immediately with suspected animal case of rabies.
- Disinfect any cage and housing of a rabid animal with soap solutions, 1% sodium hypochlorite, 2% glutaraldehyde, iodine solutions, or quaternary ammonium compounds.[3]
- Support the PEP of staff at high risk for rabies exposure.

Agent

Rabies is caused by a number of related rhabdoviruses, which are bullet-shaped RNA viruses belonging to the genus *Lyssavirus.* Lyssa viruses are unique among rhabdoviruses in their ability to replicate in a host animal's CNS.[4] Different strains of rabies virus are adapted to particular animal species and can have spillover to other species. Rabies viruses can affect any mammal.

Geographical Occurrence

Rabies viruses occur worldwide on all continents except Antarctica and Australia but in varying degrees of prevalence.

Reliable data on the prevalence in many countries are not available. Certain Pacific and Caribbean islands, including Hawaii, are considered to be free of the virus.[5] The WHO has estimated that 55,000 fatal cases occur in humans annually, with the greatest disease burden in Asia (31,000 deaths), followed by Africa (24,000 deaths).[6]

Groups at Risk

The majority of human cases occur in countries where rabies is endemic in the dog population. Travelers to such areas are therefore one group at risk of exposure and infection.

Occupational groups at risk include veterinarians, wildlife rehabilitators, wildlife management workers, zoologists, animal quarantine workers, animal control officers, and laboratory workers.

Children may be at increased risk because of their behavior of contacting wild and domestic animals. Once exposed, immunocompromised individuals may be at increased risk of contracting infection.

Unvaccinated dogs and cats with exposure to wild animals, particularly raccoons, bats, foxes, and skunks, are at increased risk of rabies exposure and infection.

Hosts, Reservoir Species, Vectors

Animals are the natural reservoir for rabies viruses. Although all mammals are considered susceptible to infection, only carnivores and bats are capable of maintaining the viral reservoir (Figure 9-98).[4] Worldwide, domestic and wild canids and other carnivores are the principal reservoir species for rabies virus. In the United States, dog rabies strain has now been eliminated largely as a result of aggressive vaccination and animal control efforts. However, the disease is now most frequently reported among wild mammals with identifiable virus variants circulating in bats, raccoons, skunks, and foxes (Table 9-51). These variants can affect other mammals including humans, cats, and dogs.[4,7] The disease is generally not reported in small rodents (e.g., squirrels, hamsters, gerbils, mice, or rats), lagomorphs (rabbits), or marsupials (opossums).

Unlike many other zoonotic diseases, animals are not believed to be subclinical carriers. Bats, canines, and other animals that develop rabies and are capable of spreading infection to other animals typically die of the disease within a short time.[8]

In the United States and Europe, oral rabies vaccine programs are used to contain and eliminate the virus from

ANIMAL RABIES CASES BY GEOGRAPHIC REGION FOR 1998 (*n*=32,342)
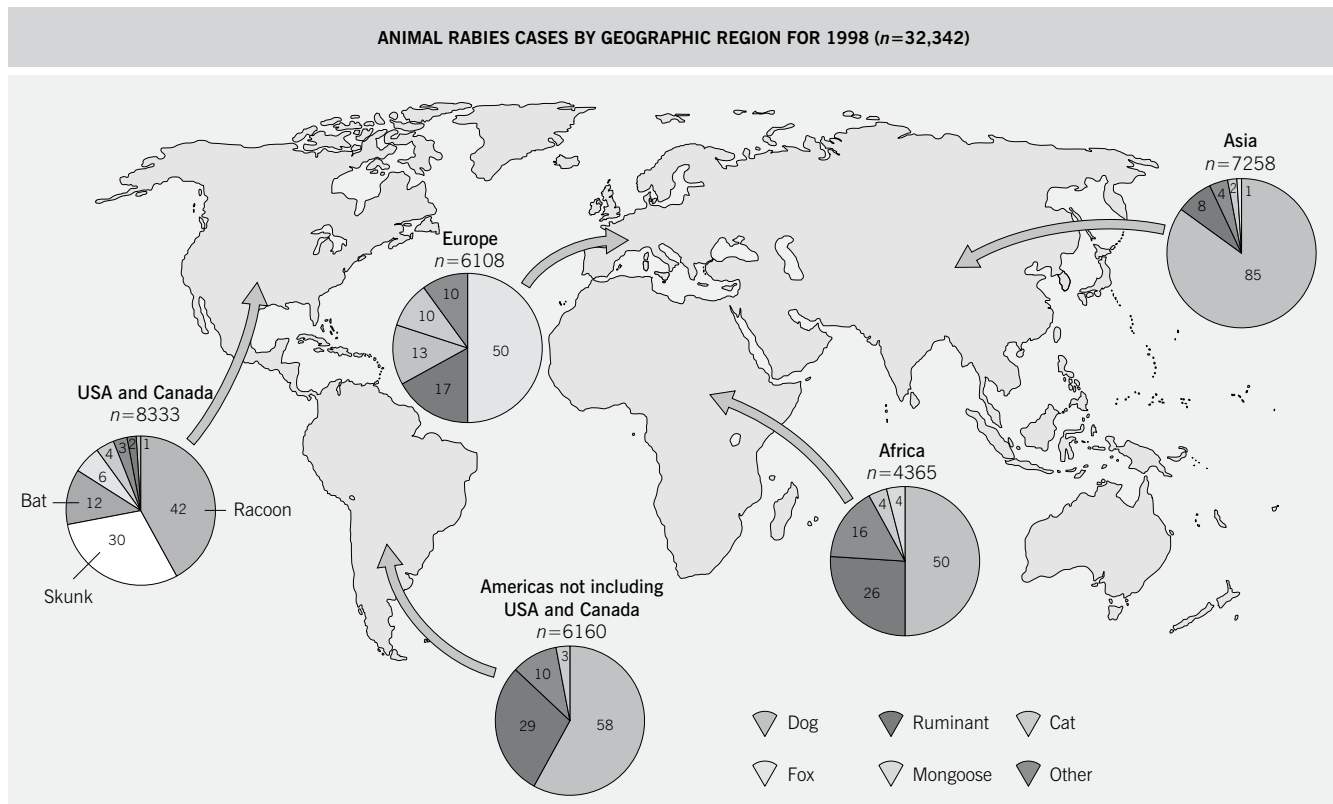
Figure 9-98 ▪ Animal rabies cases by geographic region for 1998. A total of 32,342 cases are displayed. According to World Health Organization sources in the 34th World Survey, which was based on data from 110 countries reporting from 193 members, wildlife rabies predominates in some regions, such as the United States and Canada, and dogs remain a significant reservoir in many other countries. Values shown are percentages. (NOTE: Rabies has been diagnosed among bats in Australia, but these cases are not represented here.) (From Cohen J, Powderly WG: *Infectious diseases*, ed 2, Philadelphia, 2004, Mosby Elsevier.)

Table 9-51 ■ Reported Animal Cases of Rabies in the United States (1998-2002)

Animal*	Average No. of Cases (1998-2002)	Geographical Focus†
Raccoon	2962	Eastern United States
Skunk	2257	California, upper and lower Midwest, eastern United States
Bat	1175	Entire United States, except Hawaii
Fox	443	Alaska, Texas, southwestern United States
Cat	276	Entire United States, except Hawaii
Cattle	106	Entire United States, except Hawaii
Dog	105	Entire United States, except Hawaii
Horse or mule	62	Entire United States, except Hawaii
Mongoose	58	Puerto Rico
Woodchuck	50	Eastern United States
Bobcat	30	Entire United States, except Hawaii
Sheep or goat	9	Entire United States, except Hawaii
Other wild animal	24	Entire United States, except Hawaii
Other domestic animal	3	Entire United States, except Hawaii

*All mammals are considered susceptible to rabies, and incidental (or spillover) infection from wild animal reservoirs may occur in any species.

†Rabies may occur in an exposed animal in any location; the geographical foci listed here are based on current epidemiological trends. No cases of rabies have been reported in Hawaii or in American Samoa, the Commonwealth of the Northern Mariana Islands, Guam, or the U.S. Virgin Islands.

From Rupprecht CE, Gibbons RV: Clinical practice. Prophylaxis against rabies, *N Engl J Med* 351(25):2626-35, 2004.

raccoon, skunk, fox, and coyote populations.[9] In parts of the developing world, especially Asia and Africa, the disease remains endemic in the domestic dog populations and constitutes a risk to travelers to rabies endemic countries (see Chapter 10). In Latin America, vaccination campaigns have drastically reduced cases of rabies in domestic animals and humans, but canine and wildlife rabies (including vampire bats) remains a risk.

Mode of Transmission and Life Cycle

The rabies virus enters the body by a bite, an open wound, or by contact with mucous membranes and replicates near the site of exposure (Figures 9-99 and 9-100). It then travels slowly through sensory and motor nerves to the CNS, where it causes encephalitis. Finally, it spreads centrifugally to the salivary glands and other organs through peripheral nerves. Blood, urine, and feces are not considered infectious.

Humans are usually exposed through a bite from a rabid animal. Not all humans bitten by rabid animals become infected, even in the absence of prophylactic immunization. The likelihood of transmission depends in part on the amount of virus in the saliva. Therefore very minor bites and bites through clothing may be less likely to transmit infection.[8] Transmission by contact of saliva with mucous membranes and conjunctiva is possible but less common than bite-related transmission. Both humoral and cell-mediated immunity appear to play an important role in susceptibility to infection. Immunocompromised individuals are therefore at higher risk of infection from exposure to a rabid animal.

Aerosol transmission has been reported in humans entering caves frequented by bats and in laboratory settings, but this route of exposure is considered rare. Human infection through ingestion of infected meat or milk has not been reported.[8] Person-to-person transmission has rarely been reported through corneal or organ donation.[10]

Transmission between animals results from direct contact such as bites. Dogs and other infected animals are infectious for several days (as long as 13 days has been reported with some rabies virus strains) before symptoms appear and then continue to shed virus in saliva until death; the total period of infectiousness may vary among species.[8]

Environmental Risk Factors

Worldwide, factors affecting the density of dog populations have been drivers of rabies infection risk. Increasing urbanization has brought migrants from rural areas to live closer together, often in extreme poverty, with accompanying dogs and other domestic animals that are inadequately immunized against rabies.

In countries such as the United States where wildlife populations are reservoirs, key factors include translocation of animals from a rabies-endemic area to one that has been free of rabies. For example, the epizootic of rabies in raccoons along the Eastern Seaboard of the United States occurred in part because of the transportation of rabid raccoons across state lines to be released for hunting purposes. Another factor is the increasing contact between wildlife such as bats, raccoons, skunks, and coyotes related to encroachment of suburban housing developments on wildlife habitat (Figure 9-101). Cats could play a potential role in increasing contact between rabid wildlife and human populations.

Disease in Humans

After exposure to rabies the disease has an incubation period that varies from weeks to months (usually 20 to 90 days),[8] but the incubation period has been reported to be as long as several years.[11] The distance from the exposure site to the head and neck helps determine the length of time until the onset of symptoms (Table 9-52).

Early symptoms include anxiety, headache, fever, and malaise. There may be pain, irritation, and other sensory changes around the bite. The patient often becomes excitable with sensitivity to light and sound and demonstrates aerophobia (fear of flying)[12] as well as pupil dilation and increased salivation. Over a short period (2 to 6 days), the disease progresses inexorably
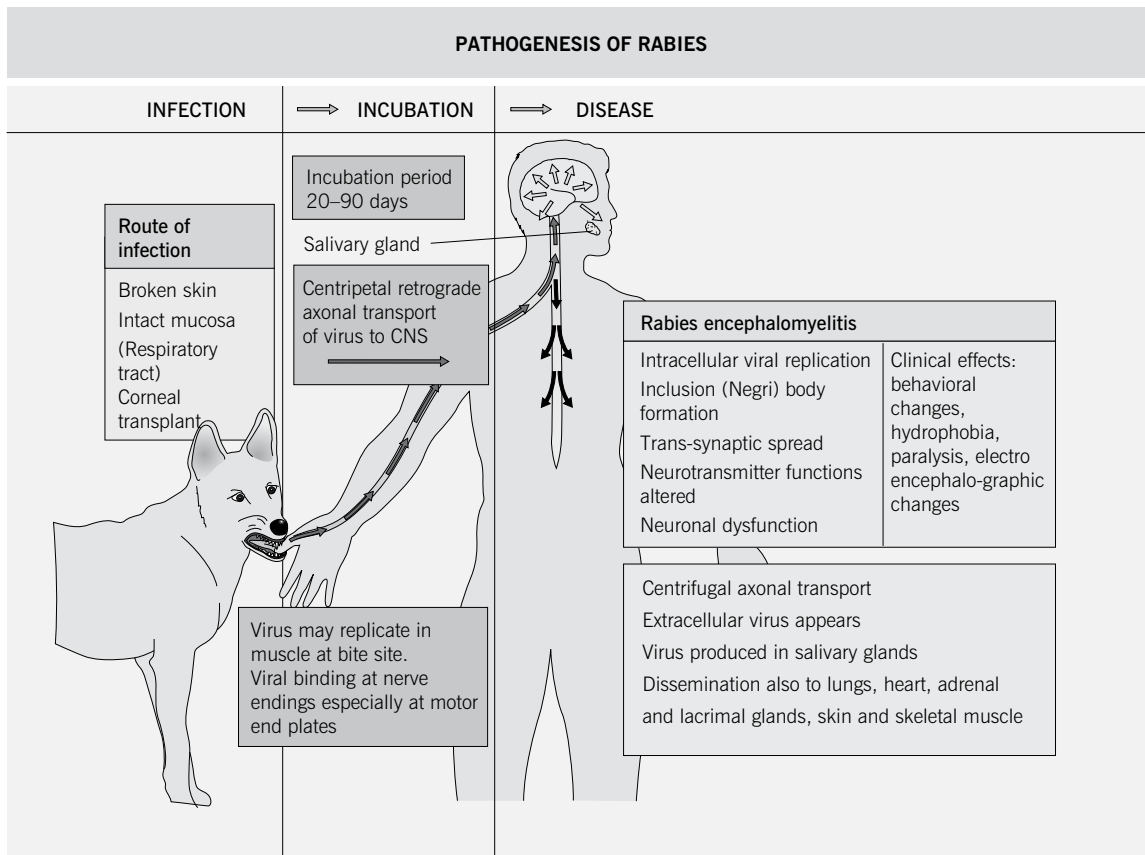
Figure 9-99 ■ Pathogenesis of rabies. (From Cohen J, Powderly WG: *Infectious diseases*, ed 2, Philadelphia, 2004, Mosby Elsevier.)

to weakness; paralysis, including spasm of the swallowing muscles, leading to inability to swallow even liquids; and fear of water (hydrophobia). Delirium and seizures can follow, as well as generalized paralysis, with death usually to the result of respiratory arrest.

In the United States, most autochthonous human rabies cases have been identified as bat rabies variants among people who did not recognize their exposure or who did not seek postexposure treatment.

Disease in Animals

The incubation period appears to vary among species (see Table 9-52) but usually last weeks to months. Once clinical signs develop, there are two major manifestations of rabies infection in animals, termed *furious rabies* and *dumb (paralytic) rabies.* Either or both forms may occur during the course of infection in a single infected animal.

Furious rabies is characterized by agitation, aggression (including unprovoked biting attacks on other animals, humans, and itself), sexual stimulation and priapism, roaming behavior, excess salivation and drooling, and abnormal vocalizations (Figure 9-102). Convulsions often develop.

Dumb rabies is marked by lethargy and paralysis. The muscle paralysis begins in the head and neck, with difficulty swallowing that may lead a dog owner to become exposed

by trying to help the animal swallow. The paralysis spreads to the extremities, leading to generalized paralysis and death (Figures 9-103 and 9-104).

Management of Rabies Exposures in Humans

Management of potential rabies exposure consists of three components: (1) wound first aid, (2) risk assessment, and (3) administration of PEP if indicated.

First-Aid

Any bite or scratch from a potentially infected animal should be cleaned immediately with soap and water and irrigated copiously with water and/or a dilute solution of povidone-iodine and water. A tetanus booster should be administered if more than 10 years have elapsed since the last vaccination (see Chapter 10).

Risk Assessment

Risk assessment and decisions regarding PEP are crucial steps in the management of rabies exposures. This requires the clinician to gather an accurate history of the exposure, including the following information that should be included in the clinical chart:
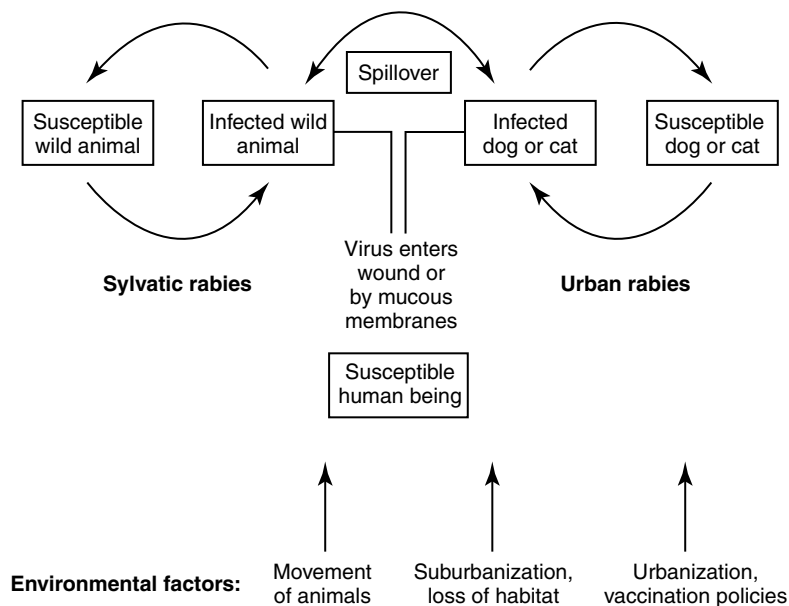
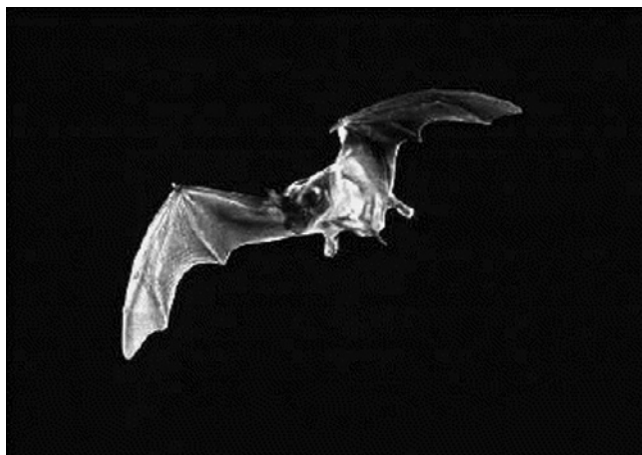Figure 9-100 ■ Rabies transmission.

Figure 9-101 ■ The brown bat *Eptesicus fuscus* ranges from southern Canada through North and Central America to extreme northern South America. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Ivan Kuzmin.)

- Current location of animal, and whether animal control or other authority is aware of incident and is going to quarantine/observe or euthanize the animal (in which case PEP can be reserved unless the test results for rabies are positive)
- Type of exposure (e.g., bite to exposed skin, bite through clothing, scratch, lick, contact with intact skin only)
- The exact location of all bites or scratches
- When exposure occurred
- Rabies immunization history of the individual
- Whether the individual is immunocompromised
- The species of animal involved, if known
- Whether the animal showed any signs of illness (including the signs of rabies listed in Table 9-52)

- Whether a bite or scratch occurred or whether the circumstances suggest an unrecognized exposure (such as a bat found in a room where someone was sleeping)
- If the animals is a domestic animal, record of immunization and name/contact information of veterinarian caring for animal

Using this information, the clinician can then assess the risk of rabies transmission and the need for PEP. Public health officials can be consulted to assist in determining the need for rabies PEP.

Figure 9-105 shows an algorithm for making this decision. The risk assessment process often requires close cooperation among the treating clinician, the public health department, animal control or veterinarian evaluating the animal, and the public health or other laboratory performing tests on the brain of the animal (if available).

Postexposure Prophylaxis

If the biting animal is tested for rabies or is a dog, cat, or ferret that can be monitored for 10 days, PEP is not necessary unless the animal shows clinical signs and subsequent test results are positive for rabies. However, if it is determined that PEP is indicated, it should be initiated as soon as possible after rabies exposure. The CDC posts updated recommendations for PEP on its Web site.[14] PEP should be started even if a prolonged time has elapsed since exposure because the incubation of human rabies can be many months. Table 9-53 lists the vaccines and antibody preparations available in the United States.

For persons who have never been vaccinated against rabies, PEP should include administration of both passive antibody (rabies immune globulin) and vaccine. For previously unvaccinated persons, the vaccine regimen consists of HDCV or PCECV, 1.0 mL IM (deltoid area), one each on days 0, 3, 7, and 14. The deltoid area should be used in adults and the anterior

Table 9-52 ▪ Rabies Infection: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Signs that May Increase Risk of Human Exposure
Humans	Handling rabies vector species	Usually 2-12 weeks, but can be years	*Prodrome:* malaise, fever, pain or pruritus at the site of bite Increasing agitation, anxiety, confusion, difficulty swallowing Hyperexcitability or paralysis Death within 2-10 days of onset of clinical signs	
Dogs	Unvaccinated, allowed unsupervised outdoors	Usually 10-60 days[8]	All species: *Furious rabies:* Irritable, attacking, biting, scratching, swallow objects, chewing, salivation	
Cats	Unvaccinated, allowed unsupervised outdoors			Furious rabies more common than paralytic form[8]
Bats	Reservoir species	Variable	*Dumb (paralytic) rabies:* Paralysis of throat and masseter muscles, inability to swallow, profuse salivation, paralysis extending to rest of body[13]	Flying in daytime, resting on ground, attacking animals, fighting, roosting in buildings, carried into the house by pet
Raccoons	Reservoir species	Variable		Loss of fear of humans, aggression, active during the day
Skunks	Reservoir species	Variable	Phonation may be altered or animal may exhibit signs of choking	Abnormal aggression (such as attacking a porcupine)
Cattle	Unvaccinated Rabies-endemic area	25-150 days		Cessation of lactation, abnormal bellowing, signs of choking
Horses	Unvaccinated Rabies-endemic area	14-60 days		Rolling on ground, resembling colic

Figure 9-102 ▪ Dog with rabies. Note open jaw and visible tongue with excessive salivary secretions resulting from the inability to swallow. (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy Centers for Disease Control and Prevention, Atlanta, Ga.)

Figure 9-103 ▪ A 4-year-old Holstein was first noticed to be abnormal when she buckled on both hind limbs coming into the parlor. Within 2 hours, she was recumbent, would not eat, and began bellowing. Cerebrospinal fluid had a lymphocytic pleocytosis. She tested positive for rabies. (From Divers T: *Rebhun's diseases of dairy cattle*, ed 2, St Louis, 2008, Saunders Elsevier.)

Figure 9-104 ■ Dog with dumb rabies, manifested as depression, lethargy, and a seemingly overly tame disposition. Domesticated animals with dumb rabies may become increasingly depressed and try to hide in isolated places, whereas wild animals seem to lose their fear of humans, often appearing unusually friendly. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

thigh can be used in children. The gluteal area should not be used for rabies immunization. Hema rabies immune globulin (HRIG, 20 international units/kg body weight) should be given just once, at the beginning of antirabies prophylaxis, and infiltrated directly around the wound site if possible.

Do not administer HRIG to a person who previously received any of the rabies vaccinations from Table 9-53 either for preexposure or postexposure purposes. Previously immunized individuals should receive only vaccine (HDCV or PCECV, 1.0 mL IM [deltoid area]), one each on days 0 and 3 after exposure.

Management of Rabies Exposure in Animals

Vaccinated dogs, cats, ferrets, and livestock that have been exposed to a known or suspected rabid animal should be revaccinated and observed in the home or farm for 45 days for signs of rabies.[15] If an unvaccinated dog, cat, ferret, or livestock animal is bitten by a rabid or potentially rabid animal, it should be euthanized or maintained in strict quarantine and monitored

Rights were not granted to include this figure in electronic media. Please refer to the printed publication.

Figure 9-105 ■ Decision tree for rabies postexposure prophylaxis. (Modified from Rupprecht CE, Gibbons RV: Clinical practice. Prophylaxis against rabies, *N Engl J Med* 351[25]:2626-35, 2004.)

Table 9-53 ▪ Rabies Vaccines and Immunoglobulin Available in the United States			
Type	**Name**	**Route**	**Indications**
Human diploid cell vaccine (HDCV)	Imovax Rabies	Intramuscular	Preexposure or postexposure
Purified Chick Embryo Cell Vaccine (PCEC)	RabAvert	Intramuscular	Preexposure or postexposure
Human rabies immune globulin	Imogam Rabies-HT	Local infusion at wound site, with additional amount IM at site distant from vaccine	Postexposure
Human rabies immune globulin	HyperRAB TM S/D	Local infusion at wound site, with additional amount IM at site distant from vaccine	Postexposure

From Centers for Disease Control and Prevention: *Rabies post-exposure.* http://www.cdc.gov/rabies/exposure/postexposure.html.

closely for signs of rabies for 6 months. Quarantine should be under the supervision of local animal control or public health authorities at an approved boarding site. If the animal victim is a valuable specimen (e.g., zoo animal), contact public health professionals to determine possible management.

Diagnosis

The diagnosis in humans can be made by biopsy of the skin at the nape of the neck (at the hairline) and by using DFA staining of frozen skin sections. Serology is also used to detect viral neutralizing antibody in serum and CSF,[12] and a PCR test is available to detect *Lyssavirus* RNA. Clinicians must work with their state public health officials to submit specimens to the CDC laboratory.

In animals, the brain of euthanized animals is examined using DFA staining (Color Plate 9-58).[2] A rapid immuno-histochemical test has recently been developed and provides high sensitivity and specificity.[16]

Treatment

Treatment in Humans

Although a number of aggressive attempts to treat symptomatic rabies infection with antiviral therapy have reported survival success in an isolated case (see Milwaukee Protocol at http://www.chw.org/display/PPF/DocID/33223/router.asp),[17] clinical rabies infection in humans remains an almost invariably fatal disease, with the principal treatment supportive intensive care.

Therefore prevention of the development of clinical disease through the use of preexposure and postexposure vaccination strategies is the mainstay of preventing rabies deaths in humans. (See *Human Rabies Prevention—United States, 2008 Recommendations of the Advisory Committee on Immunization Practices* (ACIP) at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e507a1.htm.)

Treatment in Animals

Treatment is not attempted in animals. Rabid animals are euthanized. Disinfection of the cage area should be accom-plished with disinfectants such as a 1% solution of household bleach.[2]

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ROCKY MOUNTAIN SPOTTED FEVER AND OTHER RICKETTSIAL INFECTIONS

Peter M. Rabinowitz and Lisa A. Conti

Rocky Mountain spotted fever (ICD-10 A77.0)

Other names in humans: North American tick typhus, New World spotted fever, tickborne typhus fever, São Paolo fever

Other names in animals: none

Rocky Mountain spotted fever (RMSF) and other named diseases caused by *Rickettsia rickettsii*, refer to a severe tickborne infection occurring in the Americas that is one of the deadliest known infectious diseases. In the preantibiotic era, case fatality was as high as 75%. Currently in the United States, the mortality rate is approximately 20% for untreated cases and 5% for treated cases,[1] with frequent long-term sequelae in survivors including limb amputation and neurological signs such as deafness.[2] RMSF causes similarly severe disease in dogs. The number of cases reported each year has increased since 2001, and there is evidence of expansion of host range and tick vector species. At the same time, RMSF probably remains underdiagnosed and underreported by both human health care providers and veterinarians. The diagnosis can be difficult because many patients present with nonspecific signs and may not have the classic triad of fever, rash, and tick bite. Estimation of RMSF mortality indicates that national surveillance for the disease misses some 60% of fatal cases.[3] In numerous instances, there have been temporal relationships between RMSF cases in dogs and human infection in members of the same households, demonstrating that dogs can serve as sentinels for human environmental infection risk.[4] Tragically, lack of communication between veterinarians and human health care providers has contributed to delays in diagnosis, sometimes with fatal consequences. In other cases, however, detection of RMSF in dogs has alerted human health care providers to initiate timely treatment of an infected person.[5] In addition to tick bites, a risk factor for human infection is exposure to infectious tick feces, tissues, or fluids when removing ticks from dogs. RMSF is therefore a grim reminder to human and animal health professionals of the importance of considering the diagnosis, sharing information about animal and human cases, and educating patients and clients about proper measures to prevent tickborne disease.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Characterize the risk of rickettsial disease in the community.
- Educate the public to prevent tick exposure through the following measures:
  - Avoid tick-infested areas, but if not possible, wear appropriate clothing (long sleeves, long pants, tuck pants legs into socks, and wear light-colored clothing to visualize ticks). Wash clothes with hot water.[6]
  - Use CDC-recommended tick repellents such as DEET or permethrin (apply to clothes, not skin). Be sure to follow label instructions before using any repellent.
  - Do frequent tick checks to remove even tiny immature-stage ticks. Inspect children at least once daily for ticks. When in heavily infested areas, inspect children every 3 to 4 hours.
  - Use appropriate technique to remove ticks, such as a tick removal "spoon," or wear gloves or grasp tick with tweezers as close to the skin as possible and pull gently. Applying matches, diesel fuel, nail polish, or petroleum jelly on the tick is not recommended and could lead to additional exposure to infectious material from the tick.[7]
  - Disinfect tick bites with household 70% isopropyl alcohol or 2% iodine solution. Follow up by cleaning the area, applying antibiotic topical on the tick bite site, and washing hands.
  - Implement integrated pest management techniques including landscape management (see Box 9-3) to reduce tick exposures.
- Advocate for tick prevention in dogs to reduce human exposure of the infection.

Human Health Clinicians

- Instruct patients on tick exposure prevention (see above).
- Consider the diagnosis in all patients with animal contact and/or travel to endemic countries.
- Report suspicion of disease immediately to public health authorities. See http://www.cdc.gov/ncidod/dvrd/rmsf/Case_Rep_Fm.pdf for the CDC case report form.

Veterinary Clinicians

- Recommend preventive acaricide treatment for pets.
- Notify health care professional if cases are diagnosed in dogs. Such cases could both pose a risk to humans and serve as a sentinel warning of environmental exposure risk.

Agent

The causative agent of RMSF, *Rickettsia rickettsii,* is a member of a family of closely related spotted fever Rickettsiae that are found worldwide. Rickettsiae are obligate intracellular coccobacilli with one of the smallest bacterial genomes.[8]

Because of a history of laboratory-acquired infections, many of which have proven fatal,[9] handling of *R. rickettsii* cultures requires biosafety level 3 containment. Because this bacterium was added to the select agent list, only approved laboratories can maintain cultured *R. rickettsii.*

Table 9-54 shows diseases caused by Rickettsiae in the spotted fever group. Several of these agents in addition to

Table 9-54 ■ RMSF: Diseases Worldwide Caused by Rickettsiae of the Spotted Fever Group

Agent	Disease	Geographical Distribution
Rickettsia rickettsii	Rocky Mountain spotted fever	North Central and South America
Rickettsia conorii	Mediterranean spotted fever, boutonneuse fever, Israeli spotted fever, Astrakhan fever, Indian tick typhus	Europe, Asia, Africa, India, Israel, Sicily, Russia
Rickettsia parkeri[10]	American boutonneuse fever[11]	United States, possibly South America
Rickettsia akari	Rickettsialpox	Worldwide
Rickettsia sibirica	Siberian tick typhus, North Asian tick typhus	Siberia, People's Republic of China, Mongolia, Europe
Rickettsia australis	Queensland tick typhus	Australia
Rickettsia honei	Flinders Island spotted fever, Thai tick typhus	Australia, South Eastern Asia
Rickettsia africae	African tick-bite fever	Sub-Saharan Africa, Caribbean
Rickettsia japonica	Japanese or Oriental spotted fever	Japan
Rickettsia felis	Cat-flea rickettsiosis, flea-borne typhus	Worldwide
Rickettsia slovaca	Necrosis, erythema, lymphadenopathy	Europe
Rickettsia heilongjiangensis	Mild spotted fever	China, Asian region of Russia

Adapted from Centers for Disease Control and Prevention: *Rocky Mountain spotted fever: epidemiology*. http://www.cdc.gov/ncidod/dvrd/rmsf/Epidemiology.htm.

R. rickettsii are found in the United States. *Rickettsia akari* causes rickettsialpox, a disease transmitted from mice to humans via mites that causes a vesicular skin rash, fever, and adenopathy and has been reported in urban dwellers in the eastern United States.[12] *Rickettsia parkeri* can cause a mild form of spotted fever with eschar formation at the site of a tick bite.[10,13] *Rickettsia felis* is transmitted by cat fleas to other animals, including humans, and is one of the causes of flea-borne (murine) typhus, a mild rickettsial disease.[12]

Geographical Occurrence

Despite its name, human cases of RMSF occur throughout the United States with higher incidence in the south Atlantic and western-central regions (Color Plate 9-59).[12] Even in endemic areas, infection rates of ticks with *R. rickettsii* are low. Outside the United States, RMSF occurs throughout the Western Hemisphere, with cases reported from Canada to Brazil and Argentina.

Groups at Risk

Since 1920, the disease has gone through three major cycles of emergence and has been increasing in incidence since 2000. The reasons for this are unclear.[14] The majority of reported cases in the United States occur in children younger than 15 years with a peak incidence between ages 5 and 9 years. This is believed to be due to behaviors that expose children to ticks.[15] Living near dogs carrying ticks is a reported risk factor. Laboratory workers are at risk and should use caution when handling infected material and

cultures because infection can occur by accidental parenteral exposure or through aerosols.

Hosts, Reservoir Species, Vectors

Ixodid (hard) ticks are both a disease reservoir and the vectors for RMSF, although *R. rickettsii* appears to cause mortality in ticks. At present, the two principal tick species associated with RMSF in the United States are the American dog tick (*Dermacentor variabilis*) (Figure 9-106) found east of the Great Plains, and the Rocky Mountain wood tick (*Dermacentor andersoni*) (Figure 9-107) found between the Cascade and Rocky Mountains of the west.

Figure 9-106 ■ American dog tick *(Dermacentor variabilis)*. (From Centers for Disease Control and Prevention: *Rocky Mountain spotted fever: natural history*. http://www.cdc.gov/ncidod/dvrd/rmsf/natural_hx.htm.)
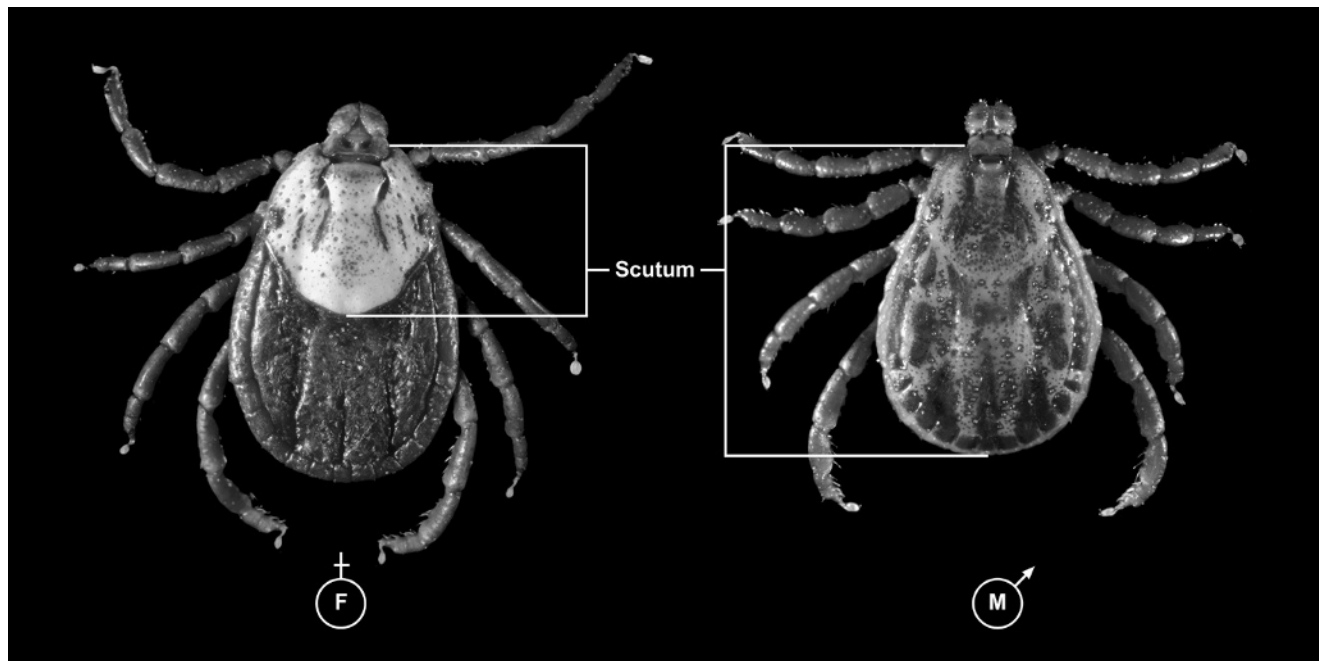
Figure 9-107 ■ Rocky Mountain wood tick *(Dermacentor andersoni).* (From Centers for Disease Control and Prevention: *Rocky Mountain spotted fever: natural history.* http://www.cdc.gov/ncidod/dvrd/rmsf/natural_hx.htm.)

Immature ticks of these two species feed predominantly on small rodents in rural and suburban environments, including the rice rat, golden mouse, white-footed mouse, and pine vole.[16] The brown dog tick (*Rhipicephalus sanguineus*), by contrast, feeds mainly on dogs and has been associated with recent human infections in the southwestern United States and is the principal vector of RMSF in Mexico (Figure 9-108).[17] In South America, the major tick vector is *Amblyomma cajennense.*

In addition to ticks, dogs and rodents can also serve as disease reservoirs for RMSF as well as infected hosts that may develop clinical disease.[18]

Mode of Transmission and Life Cycle

Once infected with *R. rickettsii*, many ticks die.[14] Those that survive remain infected for life, and female ticks can pass the infection to their offspring through transovarial transmission. The ticks have a three-stage life cycle from larva to nymph and adult (Figure 9-109). To progress from one stage to another, the tick must have a blood meal; all three stages feed on vertebrates and can transmit infection. During blood meals, *R. rickettsii* in the salivary gland of an infected tick can be injected into the dermis of the host animal, resulting in transmission. If an uninfected tick feeds on an infected host animal, the tick can become infected with the organism. For tick-to-human transmission to occur, the tick must be attached for at least 6 hours and may remain attached for days to weeks.

In addition to tick bites, humans can become infected by exposure to tick feces, tissues, or fluids by removing and crushing an infected tick, allowing secretions to contact cuts or broken skin.[8] The rickettsial organism can also be spread human to human by blood transfusion.[19]

Figure 9-108 ■ Brown dog tick *(Rhipicephalus sanguineus),* an emerging vector of Rocky Mountain spotted fever. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy James Gathany and William Nicholson.)
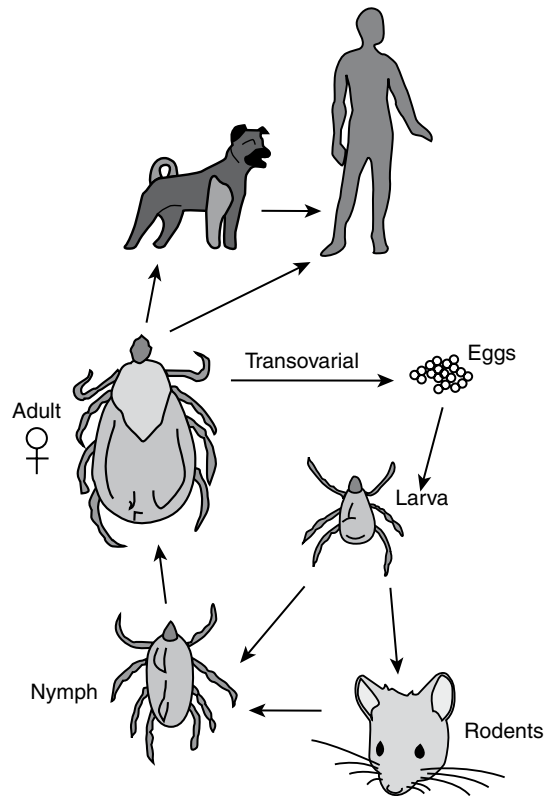
Figure 9-109 ■ Relations of tick and hosts in RMSF transmission. (From Songer JG, Post KW: *Veterinary microbiology: bacterial and fungal agents of animal disease*, St Louis, 2005, Saunders Elsevier.)

Environmental Risk Factors

Environmental factors driving the emergence of RMSF are poorly understood and are thought to vary with the ecology of the different tick reservoir species. In areas where *D. variabilis* is the principal tick reservoir, the environmental risk of RMSF has been estimated based on the density of small mammals in a particular area that serve as hosts for the tick.[16] Seasonality and climate play a strong role in human infection risk, with most cases in the United States reported between April and December when the adult ticks are more active.[15]

Disease in Humans

In the early stage of RMSF, symptoms can be nonspecific, including fever, myalgias, and headache. Only 3% to 18% of patients present at their first medical visit with the classic triad of fever, rash, and a history of a tick bite.[20] Therefore the disease should be suspected even if one of these signs is absent. Abdominal pain, nausea, and vomiting can be prominent features. The rash of RMSF occurs eventually in most cases and is often a maculopapular eruption with central petechiae that typically begins in the extremities around the wrists and ankles and spreads centripetally toward the trunk (Figure 9-110). In many, but not all, cases the rash involves the palms and soles (Color Plate 9-60).[8] Elderly and dark-skinned patients may have no visible rash (Rocky Mountain *spotless* fever).

Thrombocytopenia, elevated liver function test results, and hyponatremia are often seen. Nearly half of patients experience

Figure 9-110 ■ **A,** Exanthem of Rocky Mountain spotted fever. **B,** Close-up view. (From McGinley-Smith DE, Tsao SS: Dermatoses from ticks, *J Am Acad Dermatol* 49:363, 2003.)

hemorrhages from vasculitis rather than low platelets. In severe cases, renal failure, pulmonary edema, and respiratory distress develop. The development of neurological signs, including meningismus, neurological deficits, deafness, and photophobia, is associated with a poor prognosis. Death can occur between 8 and 15 days after the onset of symptoms if antibiotic treatment has not been started early enough in the course of the disease.[8] Survivors of severe cases may have deafness, other neurological deficits, and gangrene of the extremities.[2] Male gender, advanced age, chronic alcoholism, African American race, and glucose-6-phosphate dehydrogenase deficiency have been associated with a greater risk of fulminant disease.[1]

Disease in Animals

Dogs are often infected in endemic areas, with reported seroprevalence rates ranging from 4% to 63%, some of which could be due to cross-reactivity with other Rickettsiae in the spotted fever group.[18] Infection causes a systemic vasculitis with signs resembling some of those in humans. Within several days of tick attachment, dogs may develop fever, lethargy, lameness, and anorexia. Other signs can include edema of the scrotum, face, ears, or extremities; epistaxis and other bleeding problems, including ecchymoses and petechiae; respiratory distress; ataxia, conjunctivitis; and eye pain (Figure 9-111 and Color Plate 9-61). Neurological disease is seen in about a third of cases.[21] Cases can be mild or severe with fatality as a result of arrhythmias, shock, and disseminated intravascular coagulation. The vasculitis can result in gangrene of the extremities in severely affected dogs. The case fatality rate can be as high as 10%. In recovered animals, immunity appears to be lifelong.[19]

RMSF has rarely been reported in cats, which are believed to be much less susceptible to infection than dogs.[19] The organisms have been isolated from opossums, rabbits, chipmunks, squirrels, rats, and mice, which seem to have inapparent infection. Table 9-55 summarizes the clinical presentation of RMSF in humans and other animals.

Figure 9-111 ■ Weimaraner with chronic glaucoma in the left eye secondary to bilateral uveitis from *Rickettsia rickettsii* infection. Buphthalmia is present in the left eye, with corneal edema. (From Dziezyc J, Millichamp NJ: *Color atlas of canine and feline ophthalmology*, St Louis, 2005, Saunders Elsevier.)

Diagnosis

The differential diagnosis of RMSF in humans includes a large number of other acute febrile illnesses, including viral respiratory tract infection, gastroenteritis, other tickborne diseases including ehrlichiosis (which causes fever but no rash), thrombocytopenic purpura, and mononucleosis. Clinicians must maintain a high level of suspicion for infection in endemic areas. Clues to the diagnosis include presence of fever and rash, exposure to ticks, and occurrence of RMSF in other humans or dogs in the household or area.

Findings of thrombocytopenia, hyponatremia, and elevated transaminase values support the diagnosis. Physicians should never delay treatment waiting for laboratory confirmation. Immunohistochemistry can offer timely diagnosis but is not widely available. A PCR test is available in some centers but is not 100% sensitive. Diagnostic serology can be done but is mostly useful for retrospective diagnosis of cases. Therefore the burden falls on clinicians to

Table 9-55 ■ RMSF: Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans	*Children:* Exposures to ticks, dogs with ticks. Elderly, African American, G6PD deficiency at risk for severe sequelae	2-14 days	Early symptoms often nonspecific; fever, myalgias, abdominal pain, nausea, centripetal rash. Neurological signs, hemorrhage, respiratory and renal failure	Thrombocytopenia, elevated liver function tests, hyponatremia. PCR, immunohistochemistry, positive serological titers for confirmation. Fourfold rise in titer IFA, ELISA
Dogs	Tick exposure, mtost often in <3 years	2-14 days[19]	Fever, anorexia, lethargy, swelling, epistaxis, conjunctivitis, respiratory distress, ataxia, ecchymoses, petechiae, shock	Thrombocytopenia. Positive serology: fourfold rise in titer by IFA, ELISA, latex agglutination immunofluorescence. PCR if available

G6PD, Glucose-6 phosphate dehydrogenase.

Species	Primary Treatment	Alternative Treatment
	Table 9-56 ▪ Antibiotic Treatment of RMSF in Humans and Other Animals	
Humans	Doxycycline 100 mg PO/IV bid × 7 days or 2 days after normalization of temperature[22]	
Dogs[23]	Doxycycline 10 mg/kg PO or IV q12h × 10 days	Enrofloxacin 3 mg/kg PO, SC q12h × 10 days[19]

suspect the diagnosis and initiate antibiotics often on clinical grounds.

In dogs, the disease can be confused with canine ehrlichiosis, which responds to the same treatment. The scrotal edema may resemble that seen in brucellosis. Helpful laboratory diagnostic findings in dogs include thrombocytopenia and serology using immunofluorescence (micro-IF or direct), ELISA, or latex agglutination. PCR is available in some centers.[19]

Treatment

The treatment of choice for RMSF in adults and children is doxycycline (Table 9-56).[1] In pregnant women, the benefit may also outweigh the risk, but an infectious disease specialist and/or the patient's obstetrician should be consulted. Antibiotic treatment should never be delayed while awaiting results of diagnostic testing, because delay in treatment can lead to fatal outcomes.[20] Patients may require supportive care in intensive care settings if necessary if complications develop. Treatment in dogs usually involves inpatient care with early administration of antibiotics and supportive treatment with intravenous fluids and blood transfusion if necessary.

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RIFT VALLEY FEVER*

Tracy DuVernoy

Rift Valley fever (ICD–9 066.3)

Other names in humans: none

Other names in animals: enzootic hepatitis

Rift Valley fever (RVF) is a zoonotic arboviral disease that primarily affects ruminant livestock (cattle, sheep, and goats) and camels, but the disease can also occur in humans. Cattle, sheep, and goats appear to be particularly susceptible to infection. Animal infection is characterized by acute hepatic necrosis; increased abortions among pregnant animals; and high mortality rates in young, neonatal livestock populations. Most human infections are asymptomatic or may present as an uncomplicated influenza-like illness. However, a small percentage of human infections may result in significant neurological illness, retinitis, hepatitis, or hemorrhage progressing to death. RVF virus could potentially be introduced into the United States by an infected person or animal, especially during their viremic phase, or by an infected vector. Although RVF is currently found in Africa and the Arabian Peninsula, the virus has the potential to become established in other geographical areas owing to the abundant range of competent vectors capable of transmitting infection, the high level of viremia that develops in both infected animals and humans that allows sustainability of the virus, and the ability of the virus to adapt to different ecological conditions. However, for the virus to become established in the United States, climatic conditions must be favorable to ensure survivability of the mosquito vector, and appropriate numbers of livestock are necessary for adequate amplification of the virus. A recent publication evaluated potential pathways of RVF introduction into the United States and concluded that air transportation of a viremic civilian or mechanical transportation via aircraft or ship of an RVF-infected vector were likely pathways for introduction of RVF virus into the United States.[1] Therefore it is essential that communication among animal and human health officials be coordinated to detect this potentially devastating zoonotic infectious disease. Fortunately, a multiagency working group has been formed to discuss a research agenda, modeling efforts, and surveillance and response capabilities, among other activities, to develop a comprehensive national RVF prevention and response plan.[2]

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Be alert to the possibility of RVF introduction into the Western hemisphere and the subsequent spread by mosquito vectors.
- The irregular interval between RVF epizootics/epidemics adds to the challenge of preventing and controlling this virus. Consider increased use of techniques such as satellite remote sensing to predict global outbreaks of RVF. Environmental criteria in west and south Africa may require further evaluation to determine the validity and applicability of remote sensing imagery in these areas.
- Ensure that populations that work with livestock in endemic areas use proper precautions when butchering and processing meat.
- Use of mosquito control techniques may be highly effective in either preventing the introduction of the virus in domestic animal populations by killing immature stages of vectors[3] or control of adults during epizootic/epidemic conditions.

Human Health Clinicians

- Generally, the risk of infection in travelers is low. However, travelers to RVF-affected areas during an epizootic or epidemic should take appropriate precautions, such as using bed nets during sleep periods, using mosquito repellents, and avoiding contact with infected livestock.
- Due to the zoonotic nature of this virus, it is critical that individuals take appropriate precautions when (1) performing necropsies on suspect animals, (2) performing laboratory procedures, (3) assisting with livestock parturitions, (4) butchering possibly infected animals, or (5) performing other procedures that may place them at high risk of exposure to RVF virus.
- Report any suspected case of RVF to the appropriate local and state public health authorities. RVF cases suspected or confirmed in active duty U.S. military personnel are reportable to their respective services per the Tri-Service Reportable Events guidelines.[4]
- Use appropriate precautions especially when handling acute-phase blood products from suspect patients.
- No commercially available preventive vaccine exists for use in humans. An experimental inactivated vaccine has been used to protect laboratory and veterinary workers at high risk of RVF infection.

Veterinary Clinicians

- Consider RVF infection with increased abortions in ruminants; high mortality rates in neonatal and young

lambs, kids, and calves; and human illness particularly after heavy rains.

- In the United States, RVF is a foreign animal disease; therefore for any suspected case of RVF, it is critical to promptly notify the appropriate state and federal veterinary regulatory authorities.
- Ensure that appropriate PPE is worn when performing a necropsy on a suspect animal, when treating an ill suspect case, or when assisting with reproductive procedures. At a minimum, consider wearing a mask (to help avoid aerosols), gloves, and goggles.
- Before submitting any specimens for diagnostic purposes, contact the appropriate reference laboratory[5] to inquire about shipping requirements, diagnostic capabilities, and required specimens for submission.
- Animal disease prevention in enzootic areas may be accomplished by vaccination of susceptible livestock. The administration to small ruminants of one dose of a live attenuated virus vaccine (Smithburn strain) may confer long-term immunity and will minimize animal disease before the onset of an epizootic. However, live vaccine use may induce abortions or fetal abnormalities in pregnant animals. For disease prevention in pregnant ruminants in nonzoonotic areas, an initial dose and booster dose of a formalin-inactivated vaccine may be administered to cattle, sheep, and goats; annual revaccination is required. In addition, animal movement control is essential to prevent introduction of infected animals into new geographical locations that can support maintenance of the virus.

Agent

RVF is a mosquito-borne virus of the genus *Phlebovirus* in the family Bunyaviridae[6] (Figure 9-112). Vector transmission may occur by mechanical or biological means. It is a single-stranded enveloped RNA virus with three segments—
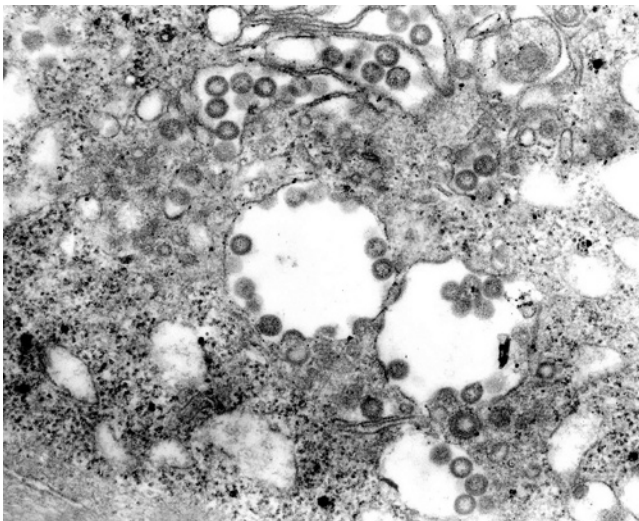

Figure 9-112 ■ This transmission electron micrograph depicts a highly magnified view of a tissue that had been infected with RVF virus. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy F.A. Murphy and J. Dalrymple.)

S (small), M (medium), and L (large)—that is readily inactivated by a pH below 6.8, lipid solvents, or strong solutions of sodium hypochlorite.[7] There is only one serotype of RVF virus. However, there are three distinct lineages: Egyptian, West African, and Central East-African.[8]

Geographical Occurrence

RVF is a disease that occurs primarily in Africa and the Arabian Peninsula. RVF was first identified in 1930 in Merino sheep along the shores of Lake Naivasha in the Rift Valley of Kenya[9] when a total of 3500 lambs and 1200 ewes died of acute hepatic necrosis after a period of excessive rainfall. Herdsmen who managed the flocks on the farm also complained of fever and arthralgia.[9] Animal epizootics, along with human epidemics, have occurred periodically since then, primarily in sub-Saharan Africa. Significant RVF outbreaks were reported in 1950-1951 (South Africa); 1997-1998 (Kenya, Tanzania, Somalia); 2006-2007 (Kenya, Tanzania, Somalia); 2007 (Sudan), and recently in 2008 (South Africa, Madagascar). The 1997-1998 outbreak in east Africa was the largest to date in terms of human disease, with approximately 89,000 human cases and 478 fatalities.[10] During the past three decades, human and animal disease has also been confirmed in western Africa and Egypt, associated with the construction of dams and subsequent flooding or irrigation projects that favor mosquito production. In 1977-1978 an outbreak that affected both humans and animals was confirmed in Egypt, the first time the virus had been identified outside sub-Saharan Africa.[11] A second occurrence of RVF occurred in Egypt in 1993. In 2000, RVF infection was reported in southern Saudi Arabia and northern Yemen along the Red Sea, the first time this virus was confirmed outside the African continent. The appearance of the virus in this new geographical location was likely due to the importation of viremic livestock from eastern Africa into the Arabian Peninsula.[12] In Saudi Arabia, 882 human cases were reported that resulted in 124 deaths,[13] and Yemen reported 1087 suspected case patients and 121 deaths.[14] Abortions in small ruminants and increased mortality in young susceptible livestock were reported concurrent with human illness.

Groups at Risk

Human groups at increased risk of RVF infection include veterinarians, abattoir workers, livestock herdsmen, and virology laboratorians as a result of occupational exposures. During epidemics, the general human population is at risk as a result of direct contact with infected livestock or animal products (including unpasteurized milk) or exposure to mosquito vectors. During epidemics, the risk of infection to travelers, soldiers, relief workers, or other individuals may be high if exposed to infected mosquitoes or to infected animals, their blood, or infected tissues.

Within animal populations, newborn ruminants (sheep, goats, and cattle) are particularly susceptible to RVF virus, resulting in a fatal infection; followed by pregnant ruminants; and then young sheep and cattle. Adult ruminants are less susceptible to infection; however, exotic breeds are more susceptible and exhibit more pathology. Horses and swine are even less susceptible.

Figure 9-113 ■ Female *Aedes* mosquito in the process of acquiring a blood meal from her human host. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Frank Hadley Collins, University of Notre Dame).

Figure 9-114 ■ Transmission and life cycle of Rift Valley fever infection, including the ecological drivers for outbreaks.

Hosts, Reservoir Species, Vectors

Many different species of mosquitoes are involved in the transmission of RVF; the virus has been isolated from more than 30 species among six genera of mosquitoes (Figure 9-113).[15] Additionally, RVF virus has been isolated from flies and *Culicoides*, biting midges. However, a few arthropod species play key roles in the transmission during epidemics/epizootics and during the period between these disease-occurring events. The reservoir of RVF in sub-Saharan Africa is thought to be *Aedes* mosquitoes (*Ae. vexans*, *Ae. mcintoshi*, and *Ae. dalzieli* primarily) that can transovarially transmit RVF virus to their drought-resistant eggs,[16] thereby allowing the virus to remain dormant and survive for long periods in soil depressions pending significant rainfall.[17] This vertical transmission is critical in maintaining RVF in endemic/enzootic areas.

The natural reservoir of RVF virus is currently unknown. The role of wildlife in the perpetuation, maintenance, and circulation of virus during the interepizootic period is also not clearly understood.[18] Experimentally, rhesus macaques[19] and inbred laboratory mice[20] have been shown to demonstrate clinical signs of disease once infected with RVF virus.

Mode of Transmission and Life Cycle

Once appropriate levels of rainfall occur and land depressions fill with water, dormant RVF-infected *Aedes* mosquito eggs hatch and adults emerge (Figure 9-114) and, acting as primary vectors, feed on susceptible livestock (Figure 9-115). Infected livestock amplify the virus, developing significant viremias—up to $10^{8.0}$ plaque-forming units (PFUs)/mL[1]— and contribute to epizootic maintenance, circulation, and spread of the virus via secondary vectors (*Culex* mosquitoes) that feed on livestock and perpetuate the infection. Intense virus activity may last for 6 to 12 weeks.[21]

Human infection can occur after a bite from an infected mosquito or by mechanical transmission from other insects. However, most infections occur as a result of direct or indirect exposure to infected blood, tissues, or body fluids of infected animals; by the butchering or slaughtering of infected animals; or by performing veterinary or obstetrical procedures
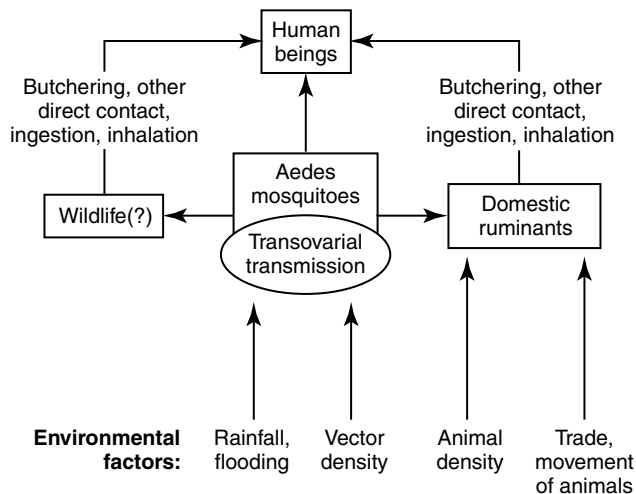

Figure 9-115 ■ Epidemiological investigation in Saudi Arabia that had been initiated as a response to a Rift Valley fever outbreak in the region. These goats were penned in a village that was within the geographical parameters of the investigation. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Abbigail Tumpey.)

on infected animals. In this way, RVF can be considered an occupational disease of individuals who work with livestock (see Chapter 12). Infection occurs by way of inoculation or aerosolization and inhalation of virus. Infection may also occur subsequent to consuming unpasteurized milk from

infected animals. Direct human-to-human horizontal transmission has not been documented; however, two recent articles describe case reports of vertical transmission of RVF infection from pregnant mother to fetus.[22,23] Direct animal-to-animal transmission has not been reported.

Environmental Risk Factors

Epizootics and epidemics occur at irregular internals (ranging from 3 to 15 years)[21,24] and typically follow significant rainfall that floods areas of sub-Saharan eastern and southern Africa, subsequently hatching dormant floodwater *Aedes* mosquito eggs.[25] However, in more arid areas of Africa, the interval may approach every 15 to 35 years. The frequency depends on rainfall and other climatic conditions that favor large vector populations, susceptible animal species populations, and the existence or introduction of virus in the geographical area. For these reasons, satellite imagery may offer an early warning of environmental conditions that favor disease occurrence, allowing a few months' lead time to mitigate disease impacts in both animals and humans. The National Aeronautical and Space Agency (NASA) and other agencies have used satellite imagery remote sensing to create predictive risk maps for RVF outbreaks. This remote sensing approach incorporates measures such as the normalized difference vegetation index (an indicator of recent rainfall and green vegetation), sea surface temperature, and rainfall.[26] In October 2006, this technology assessed such environmental conditions and accurately forecasted an outbreak of RVF in Kenya before an actual confirmed outbreak in December 2006. Figure 9-116 shows an example of an environmental risk map for RVF produced by NASA.

The outbreak in Egypt along the Nile Delta in 1977-1978 was a concern because the virus had not been previously identified north of the Sahara Desert. However, conditions that favored an outbreak included construction of the Aswan High Dam and flooding of the Nile River delta[24] and a concurrent large outbreak in East Africa. Another incident following a change to the environment occurred in western Africa in Mauritania and Senegal in 1987. One year after the construction of the Diama Dam and subsequent flooding of the Senegal River basin, an outbreak of RVF affected both humans and other animals.[24,27] Despite the linkages between recent flooding and rainfall to many RVF outbreaks,
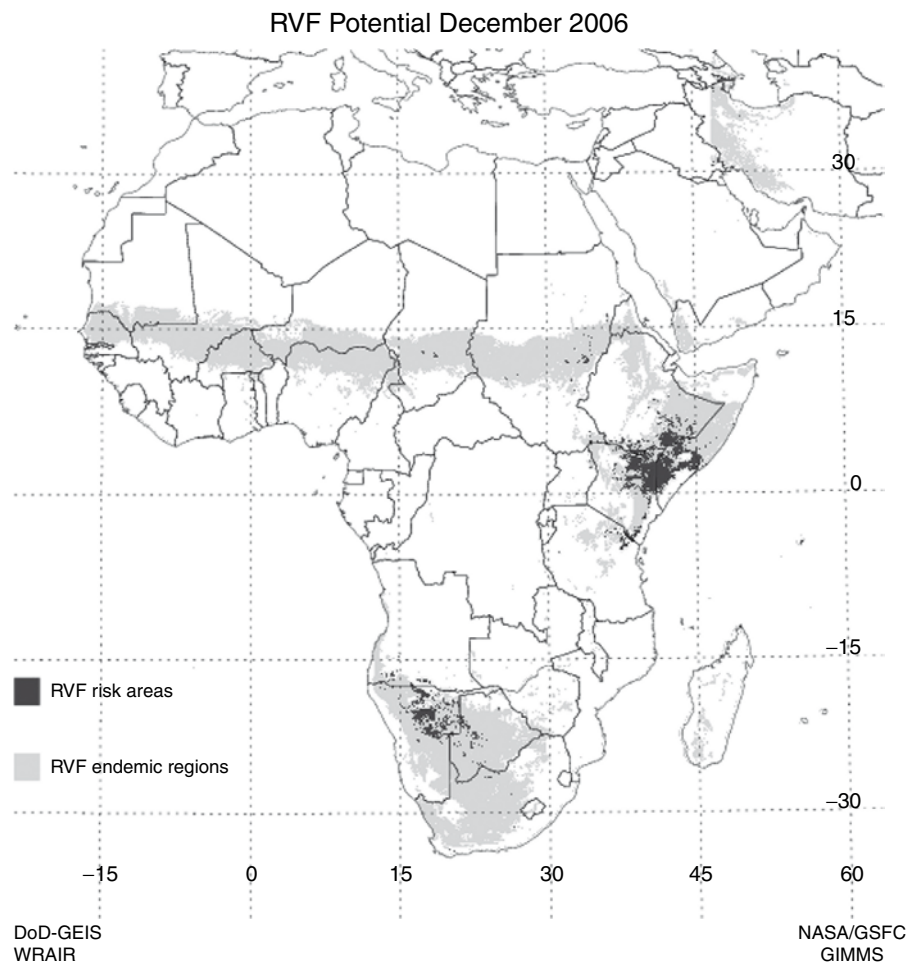

Figure 9-116 ■ Risk map for Rift Valley fever based on normalized difference vegetation index (NVDI, an indicator of green vegetation). (From U.S. Department of Defense, Global Emerging Infections Surveillance and Response System: *Rift Valley fever (RVF): monthly updates: state of climate and environmental conditions*. http://www.geis.fhp.osd.mil/GEIS/SurveillanceActivities/RVFWeb/monthlypages/0612.htm.)

not all follow this pattern because some outbreaks appear to be related to the trade and movement of infected viremic domestic animals across borders.[11,12,24]

Disease in Humans

In humans, the incubation period of RVF is 2 to 6 days; RVF produces an influenza-like illness with fever, headache, arthralgia, and myalgia.[28] Viremic titers are high after infection and can persist for more than 1 week. Recovery is usually complete; however, complications or a more serious form of the disease can manifest as three different syndromes.

Retinitis

Between 0.5% and 2% of human RVF infections result in retinitis; onset occurs 1 to 3 weeks after the initial symptoms. The disease may resolve within 10 to 12 weeks; however, permanent vision loss may occur in 1% to 10% of those with this syndrome. Death is uncommon in those infected with the ocular form of RVF.

Meningoencephalitis

Meningoencephalitis occurs in 1% of those infected with RVF, generally 1 to 4 weeks subsequent to the initial symptoms. Patients may report an intense headache, photophobia, memory loss, and confusion; convulsions and coma may ensue. The death rate is low; however, neurological sequelae are common in individuals with this form of RFV infection.

Hemorrhagic Fever

Fewer than 1% of those infected have hemorrhagic fever, which typically develops 2 to 4 days after illness onset; jaundice is generally observed first. Additional hepatic involvement manifests as hemorrhage, hematemesis, melena, ecchymoses, and persistent bleeding from other sites. Death occurs 3 to 6 days after onset of these symptoms; the case fatality rate may approach 50%.

The overall case fatality rate of RVF infection in humans typically ranges from 0.5% to 1.0%. However, during a recent outbreak in Kenya, the case fatality rate was 29% among 404 confirmed or probable cases during a 3-month period from November 30, 2006, to January 25, 2007.[29] The high case fatality rate was likely due to severe illness and the hemorrhagic fever presentation of many of those infected.

Disease in Animals

RVF causes morbidity and mortality in many different livestock species. In Africa, exotic livestock breeds are more susceptible to infection than indigenous breeds such as *Bos indicus*.[21] In pregnant ungulates, abortion is the most common clinical sign. Abortion may occur at any time during the gestation period and the rate may approach 100% in infected pregnant ewes. In newborn lambs, kids, and calves after an incubation period as short as 12 hours, the most prevalent clinical sign is death, preceded by fever. Mortality rates can approach close to 100% in some species. Older animals may demonstrate weakness, anorexia, listlessness, and a nasal discharge. Infection in adult cattle and small ruminants is often subclinical; however, some animals may develop fever, anorexia, bloody diarrhea, and a mucopurulent nasal discharge. Adult camels do not demonstrate clinical signs of illness; however, they do abort. The mortality rate in adult livestock may range from 10% in cattle to 20% in sheep. Infection and disease in domestic animals causes considerable economic losses because of the significant number of abortions, the high rate of mortality in young ruminants, and the disruption in trade and exports that are associated with epizootics.

Although some species of wildlife have detectable antibody levels against RVF, such infections are generally subclinical. One recent publication reported that of 16 different wildlife species sampled during 1999-2006 in Kenya, seven had detectable neutralizing antibodies against RVF. These data suggest that native wildlife are indeed infected with RVF[30]; however, additional studies are needed to determine their role as reservoirs or amplifiers of the virus. Table 9-57 shows the comparative presentation of disease in humans and other animals.

Diagnosis

In humans, RVF should be suspected in the differential diagnosis when the following conditions are observed: influenza-like illness, retinitis, and/or meningoencephalitis and hemorrhagic fever in individuals with livestock contact, especially in the setting of high mosquito vectors associated with recent flooding or after significant rainfall. Cases of abortion in ruminants also support the diagnosis in humans. Recent human infection is determined by serology to detect IgM antibodies by ELISA; by virus isolation during the acute, viremic phase; or by RT-PCR to detect viral antigen.[28]

In animals, the differential diagnoses for a "storm" of abortions in pregnant ruminants and a high mortality rate among young/neonatal ruminants includes a number of diseases such as brucellosis, ovine enzootic abortion, Nairobi sheep disease, rinderpest, peste de petit ruminants, vibriosis, ephemeral fever, Wesselsbron disease, trichomonas, and heartwater. To detect RVF infection in animals, heparinized blood may be analyzed for virus isolation, especially during the acute phase when virus levels are elevated. Acute and convalescent sera can be used to detect a rise in antibody levels by ELISA or hemagglutination inhibition; antibody is present within 6 to 7 days after infection.[31] Tissue specimens may also be submitted for virus isolation as long as they are not formalinized. Electron microscopy may be used to detect viral particles in tissue specimens or RT-PCR can be used to detect viral antigen. For histopathological review, the best necropsy samples to submit in 10% buffered formalin include the spleen, liver, and brain (particularly from aborted fetuses).

Treatment

Asymptomatic human infections typically do not warrant treatment. For individuals with more significant illness, treatment is supportive. Although there are no specific antivirals that are effective once symptoms occur, antivirals such as ribavirin and interferon-alpha have shown some promise in treatment trials involving nonhuman primates. There is no treatment available for infected animals.

Table 9-57 ▪ Clinical Presentation of Rift Valley Fever in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Diagnostic Findings
Humans	Direct or indirect contact with infected livestock/products, aerosolization via slaughtering, mosquito bites	2-6 days	Asymptomatic or mild influenza-like illness More severe disease (<2% of cases): retinitis, meningoencephalitis, or hemorrhagic fever	IgM serology (ELISA), RT-PCR, virus isolation
Neonatal and young domestic ruminants	Exposure to infected mosquitoes	12 hours-3 days	Fever, anorexia, weakness, listlessness, diarrhea, mucopurulent nasal discharge, high mortality rate	Virus isolation, RT-PCR, histopathology
Adult domestic ruminants		1-3 days	Abortions Subclinical in nonpregnant animals; however, some develop fever, anorexia, ptyalism, diarrhea	ELISA to detect IgG and IgM, virus isolation, RT-PCR
Wild ruminants		Unknown	Subclinical; however, may abort (African buffalo)	Serological evidence of antibodies

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SALMONELLOSIS

Peter M. Rabinowitz and Lisa A. Conti

Salmonellosis (ICD-10 A02)

Other names in humans: Salmonella *infection*

Other names in animals: salmonellosis, songbird fever, fowl typhoid

The genus *Salmonella* was named after Dr. Daniel Salmon, a noted veterinary pathologist. As an infectious disease challenge, it epitomizes the importance of human health and animal health clinicians working collaboratively. It is one of the most common causes of infectious diarrhea and gastroenteritis. At the same time, its true importance is probably underestimated; it is thought that fewer than 1% of cases in industrialized countries, and even fewer in developing countries, are reported.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Educate clinicians that *Salmonella* infection is reportable to public health authorities.
- Educate the public about the risk to children and others of *Salmonella* poisoning from food.
- Use good kitchen hygiene; be particularly careful with foods prepared for children, the elderly, or immunocompromized individuals.
- Thoroughly wash raw vegetables and fruits.
- Do not eat foods made with raw eggs or unpasteurized milk products.
- Cook poultry, ground beef, and eggs thoroughly.
- Breastfeeding prevents salmonellosis and many other health problems in infants.[1]
- Educate the public, veterinarians, and human health clinicians on CDC guidelines for prevention of reptile and other animal associated salmonellosis; such educational messages have proven effective[2] (Box 9-6; see also http://www.cdc.gov/healthypets/spotlight_an_turtles.htm).[3]
- Ensure that local petting zoos and other areas where the public has contact with animals have policies and procedures for reduction of infection risk such as handwashing stations.
- Ensure that local pet stores are not selling small turtles.
- Disinfect with 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde, or iodine solutions.

Human Health Clinicians

- The disease is reportable to public health authorities.
- Ask about a history of pet and other animal contact in all patients presenting with gastroenteritis and other *Salmonella* infections.

BOX 9-6	*RECOMMENDATIONS FOR PREVENTING TRANSMISSION OF* SALMONELLA *FROM REPTILES AND AMPHIBIANS TO HUMANS*

- Pet store owners, health care providers, and veterinarians should provide information to owners and potential purchasers of reptiles and amphibians about the risks for and prevention of salmonellosis from these pets.
- Persons at increased risk for infection or serious complications from salmonellosis (e.g., children younger than 5 years and immunocompromised persons) should avoid contact with reptiles and amphibians and any items that have been in contact with reptiles and amphibians.
- Reptiles and amphibians should not be allowed in households that include children younger than 5 years or immunocompromised persons. A family expecting a child should remove any pet reptile from the home before the infant arrives.
- Reptiles and amphibians should not be allowed in child care centers.
- Persons always should wash their hands thoroughly with soap and water after handling reptiles and amphibians or their cages.
- Reptiles and amphibians should not be allowed to roam freely throughout a home or living area.
- Pet reptiles and amphibians should be kept out of kitchens and other food-preparation areas. Kitchen sinks should not be used to bathe reptiles and amphibians or to wash their dishes, cages, or aquariums. If bathtubs are used for these purposes, they should be cleaned thoroughly and disinfected with bleach.
- Reptiles and amphibians in public settings (e.g., zoos and exhibits) should be kept from direct or indirect contact with patrons except in designated animal-contact areas equipped with adequate handwashing facilities. Food and drink should not be allowed in animal contact areas.

From Centers for Disease Control and Prevention: *Diseases from reptiles*. http://www.cdc.gov/healthypets/animals/reptiles.htm. Accessed January 16, 2009.

- Counsel pregnant women to remove any reptiles kept as pets in the house.[4]
- Counsel immunocompromised patients, young children, older adults, and patients with sickle cell anemia to avoid contact with puppies and kittens that have diarrhea and with any reptiles, baby chicks, or ducklings.

Veterinary Clinicians

- Counsel pet owners not to feed dogs and cats raw meat diets and to wash hands after handling animals, feces, and animal food treats.
- Counsel owners to practice good sanitation of cages, runs, feed and water dishes; proper storage of feed and feed utensils; reduce overcrowding situations; isolate and screen for illness in new animals.
- Ensure that appropriate infection control procedures are being followed by staff in veterinary care facilities.
- Counsel clients that immunocompromised individuals, infants, and older adults should avoid contact with reptiles, baby chicks, and ducklings.

- Counsel owners who want to give antibiotics prophylactically to their pets that that practice is ill advised due to the possibility of selecting for antibiotic-resistant strains.
- Be aware of CDC recommendations about reptiles and pets; see http://www.cdc.gov/healthypets/spotlight_an_turtles.htm.
- Counsel reptile owners on proper handwashing after pet handling and not bathing reptiles in bathtubs or sinks (Figure 9-117).[5]

Agent

Salmonella are gram-negative, facultative anaerobic rod-shaped bacteria belonging to the family Enterobacteriaceae that colonize the small intestine. There are thousands of distinct serovars, many adapted to particular animal species. In humans, the most common agents are *S. typhimurium* and *S. Enteritidis. Salmonella* Typhi, the causative agent of typhoid fever, and *S.* Enteritidis serotype Paratyphi are found only in humans. Most *Salmonella* serovars have animal reservoirs

and are potentially zoonotic. β-Lactamase–mediated antimicrobial resistance is common. Antibiotic resistance in *Salmonella* species has been linked to the use of antibiotics in animal agriculture.[6]
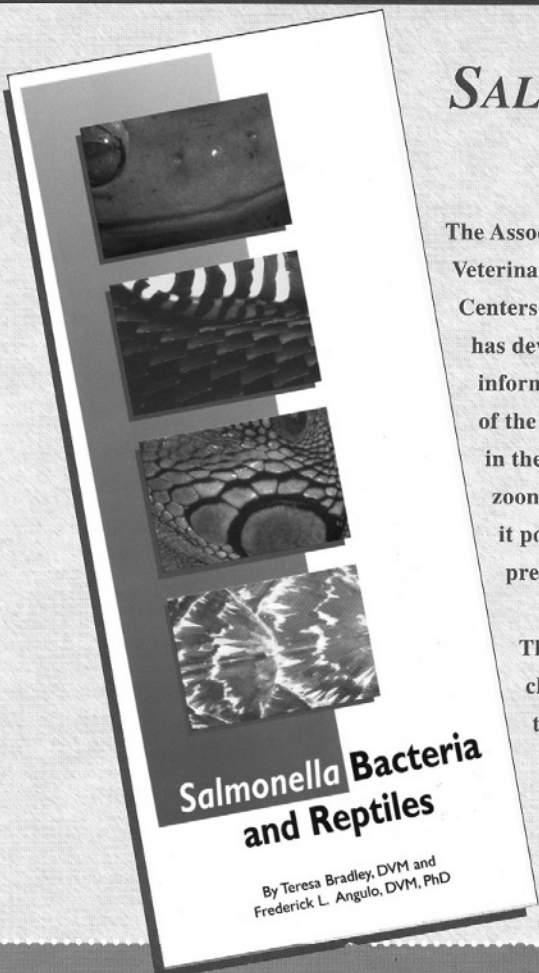
Geographical Occurrence

Salmonella occur commonly worldwide in both animals and humans. *S.* Enteritidis is the most common species, followed by *S. typhimurium.*

Groups at Risk

Young children appear to be at increased risk of significant infection. Playing in sandboxes has been linked to risk in children.[7] Older adults and immunocompromised individuals are also considered high-risk groups. Individuals with HIV infection are at risk of recurrent septicemia. Patients with sickle cell disease can develop focal infections such as osteomyelitis. Other risk factors include achlorhydria, antacid treatment, antibiotic therapy, and malnutrition.
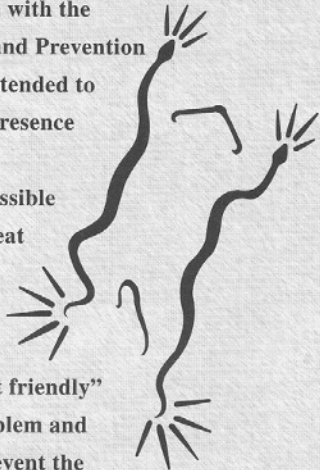

Figure 9-117 ▪ Association of Reptilian and Amphibian Veterinarians *Salmonella* brochure. Clients must be warned of potential risks of reptile ownership. (From Mader DR: *Reptile medicine and surgery*, ed 2, St Louis, 2006, Saunders Elsevier.)

Ownership of reptiles and other pets (including rodents) is a risk factor for infection (Figures 9-118 and 9-119). An estimated 4% of the U.S. population owns reptiles, and a FoodNet study estimated that 6% of reported salmonellosis cases in the United States were attributable to reptile and amphibian ownership.[8]

Salmonellosis can also be an occupational disease. An outbreak occurred among 45 workers in companion animal veterinary medical facilities, and lack of proper biosafety precautions was considered the cause.[9] Other cases have occurred among veterinary pathologists performing necropsies,[10] workers producing poultry vaccines,[11] and workers exposed to raw meat.[7]

Newborns and debilitated animals are at risk of more severe disease. Crowding, boarding, mixing, and malnutrition are stressors that predispose many animals to infection. Group housing is associated with higher rates of infection in cats. Feeding dogs and cats raw meat has been found to increase the risk of infection.[12] Dry pet food and pig ear dog treats have been found to be contaminated and pose a risk to pets and their owners.

Hosts, Reservoir Species, Vectors

Animals are the natural reservoir for all *Salmonella* species except *S.* Typhi and *S.* Paratyphi. A wide range of species may be asymptomatic carriers of *Salmonella*, including dogs, cats, birds (including poultry), cattle, swine, horses, reptiles and amphibians, wildlife (including rodents), carnivores, and even crustaceans. Poultry are considered one of the principal reservoirs for *Salmonella* organisms and have harbored hundreds of different serovars.

Prevalence rates of subclinical infection in dogs is between 1% and 35%.[13] A recent survey found infection rates as high as 50% in group-housed cats.[14] Infected migrating songbirds can result in epidemics in bird-hunting cats.

Reptiles have rates of subclinical infection as high as 90% and pose a significant risk of transmission to pet owners and animal handlers in zoos and pet stores. The sale or distribution of small turtles has been illegal in the United States since 1975 because children were more likely to treat smaller turtles as toys and put them in their mouths.[15] However, pet turtles continue to be sold illegally and have caused recent outbreaks of salmonella infection.

Mode of Transmission and Life Cycle

Salmonella is considered primarily a foodborne disease, usually of animal origin. Food or water that is contaminated with feces from an infected animal is then ingested by a susceptible human host (Figure 9-120). Person-to-person spread can occur by the fecal-oral route or by food handlers who are shedding organisms and contaminate ready-to-eat food items.

Infection can occur sporadically or in large outbreaks involving thousands of individuals with a common exposure.[16] Contaminated peanut butter and peanut paste was the source of a multistate outbreak of *S.* Typhimurium infection for people and pets through contamination of processed foods and pet treats.[17]

An outbreak in humans and dogs in the United States and Canada was linked to contaminated raw food pet treats; presumably the owners did not wash their hands adequately after handling the treats.[18] Coprophagia and scavenging spreads the bacteria. Zoonotic transmission can also occur by direct contact with the feces of an infected animal. Animals with acute illness shed copious numbers of *Salmonella* in feces.
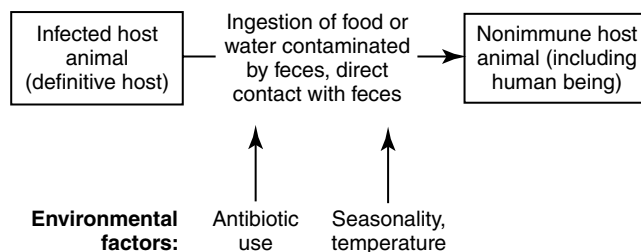

Figure 9-118 ■ Young boy holding a box turtle. Turtles and other reptiles and amphibians are sources of *Salmonella* infection, which is potentially dangerous to children. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Photo courtesy James Gathany.)

Figure 9-119 ■ A young child appropriately washing his hands after handling a turtle, which could have been contaminated with *Salmonella*. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Photo courtesy James Gathany.)

Figure 9-120 ■ The life cycle of salmonellosis.

Environmental Risk Factors

Salmonella can persist for months in food, feces, soil, and water given appropriate environmental conditions. The bacteria are resistant to dehydration and salinity. Survival in composted manure is as short as a week, and pasteurization kills *Salmonella* organisms.[19] Seasonality appears to affect the occurrence of disease, with more cases reported in the spring and summer.[20]

Disease in Humans

Human infection with non-typhi *Salmonella* can take a number of forms, including gastroenteritis, bacteremia and vascular infection, localized infection, and chronic carrier state (Figure 9-121).[21] Gastroenteritis in an immunocompetent adult often manifests as self-limited diarrhea. The incubation period is 6 to 72 hours. The principal symptoms are acute onset of diarrhea, often accompanied by nausea, abdominal pain, headache, fever, myalgias, vomiting, and malaise. Dehydration, sometimes severe, may occur, especially among the young and elderly. In most cases, symptoms resolve within 3 to 7 days. Diarrhea lasting longer than 10 days should suggest another diagnosis. However, convalescent patients may shed bacteria for weeks or months, and a chronic carrier state can occur in adults.[21]

Certain strains of *Salmonella* are particularly pathogenic in humans, such as *S. choleraesuis* and *S. dublin*, which can cause prolonged bacteremia, invasive disease, and death.[6,22] However, other *Salmonella* serotypes can also cause bacteremia, which can be accompanied by endovascular infection.

Localized infection can occur in 5% to 10% of cases of bacteremia. Specific infections include osteomyelitis, septic arthritis, endocarditis, meningitis, and pneumonia. Patients with sickle cell anemia are more susceptible to some of these conditions.[21]

In patients with AIDS and other immunocompromised individuals, bacteremia is common and often includes severe complications including localized infections, fulminant diarrhea, and death.

Disease in Animals

In adult cattle, sheep, pigs, and horses the disease takes three forms: subclinical carriage, mild clinical disease, or acute onset of fever and diarrhea, often with dehydration, abdominal pain, and sometimes bacteremia and death (Color Plates 9-62 to 9-64). Abortion may be the presenting sign of infection. Malabsorption and pneumonia may be part of the clinical syndrome. Newborn calves, lambs, piglets, and foals are more likely to develop septicemia (Figure 9-122). Outbreaks occur on farms, often precipitated by crowding, stress, calving, and mixing in feedlots.[19] Outbreaks also occur in equine hospitals.[19]

In dogs and cats, the disease is often subclinical. In puppies, kittens, or adults stressed by hospitalization, boarding, or concurrent disease, acute diarrhea with fever and septicemia can occur. Complications can include development of chronic infection and recurrence of disease under stressful conditions.

In caged birds, clinical salmonellosis is rare but may be seen in immunocompromised or stressed animals (songbird fever) (Color Plate 9-65). Although poultry often do not manifest disease, two serovars adapted to poultry, *S.* Pullorum and *S.* Gallinarum, cause serious losses on farms worldwide. Pullorum disease causes anorexia and diarrhea in chicks and has a high mortality rate. Fowl typhoid due to *S.* Gallinarum is a disease of adult birds (Figure 9-123).

Reptiles can shed *Salmonella* without clinical signs; however they may develop abscesses (Figure 9-124). Infection in wildlife is common, and clinical cases have been seen even in manatees and beluga whales.[19] Table 9-58 provides clinical presentations of salmonellosis in humans and other animals.
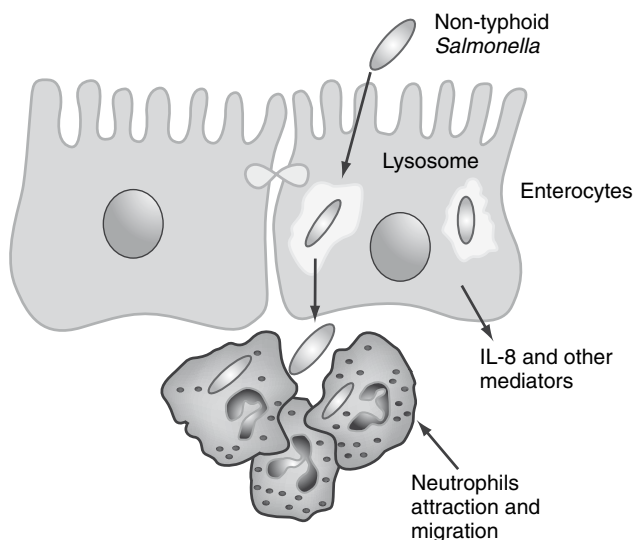
Non-typhoid *Salmonella* gastroenteritis

Figure 9-121 ■ Pathogenesis of *Salmonella* gastroenteritis. (Adapted from Kliegman RM, Behrman RE, Jenson HB et al: *Nelson textbook of pediatrics*, ed 18, Philadelphia, 2007, Saunders Elsevier.)

Figure 9-122 ■ One day's death toll of neonatal calves from a dairy farm with high mortality rates in cattle of all ages during an epidemic caused by a highly virulent *Salmonella typhimurium* strain. (From Divers TJ, Peek SF: *Rebhun's diseases of dairy cattle*, ed 2, St Louis, 2008, Saunders Elsevier.)
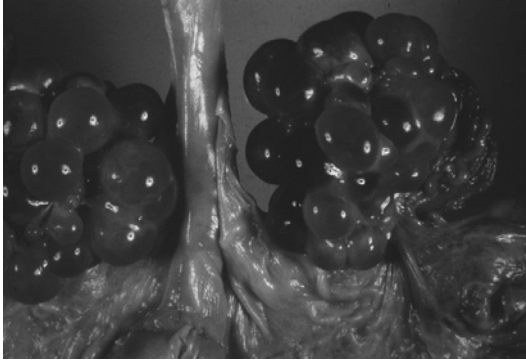
Figure 9-123 ■ Avian salpingitis as a result of *Salmonella* infection. (From Songer JG, Post KW: *Veterinary microbiology: bacterial and fungal agents of animal disease*, St Louis, 2005, Saunders Elsevier. Courtesy Raymond E. Reed.)
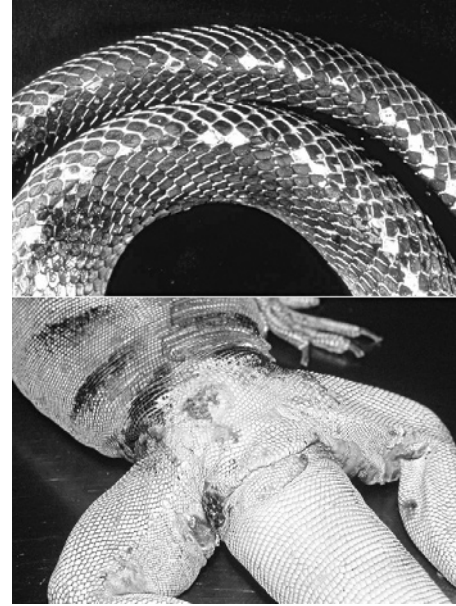
Diagnosis

Gastroenteritis in humans due to *Salmonella* can resemble other bacterial, viral, and protozoal forms of diarrhea. The incubation period and the presence of fever and often bloody stools can help narrow the differential diagnosis, and definitive diagnosis is made by bacterial culture

Figure 9-124 ■ *Salmonella* species dermatitis in an Eastern Indigo snake (*Drymarchon cooperi*, *top*) and green iguana (*Iguana iguana*, *bottom*). (From Mader DR: *Reptile medicine and surgery*, ed 2, St Louis, 2006, Saunders Elsevier. Photograph courtesy D. Mader.)

Table 9-58 ■ *Salmonella* Infection: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans (*S.* Typhimurium, *S.* Enteritidis, others)				
Gastroenteritis	Contaminated food, immunocompromised status, children at increased risk, prior antibiotic treatment, contact with animals	6-72 hours	Diarrhea, often with mucus or blood; abdominal cramping, fever	Fecal leukocytes, organisms seen on Gram stain, dark-field, or phase-contrast microscopy of feces, stool culture
Bacteremia	HIV/AIDS, other immuno-compromised status, sickle cell anemia, older age		Fever, localized infection (bone, joint vascular, CNS, other)	Blood culture, culture of localized infection
Dogs, cats	Puppies and kittens at increased risk; raw meat diets; recent hospitalization, concurrent disease/immunocompromised status, pregnant dogs	3 days[19]	Acute diarrhea with septicemia, pneumonia, abortion, chronic febrile illness, conjunctivitis (cats)	Leukopenia with left shift, fecal culture, fecal leukocytes, blood culture
Cattle, sheep, swine, horses	Young animals at increased risk, crowding, malnutrition, mixing, stress, rodents, Infected feed, contact with sick animals	Variable, 6-24 hours in horses	Acute septicemia in newborns[19] Acute or subacute enteritis in adults and young animals with fever, watery diarrhea, decreased milk production, abdominal pain, abortion Chronic enteritis (pigs and cattle)	Leukopenia (horses)
Caged birds	Clinical disease with stress, immunocompromised status			
Poultry	Chicks at increased risk for *S.* Pullorum	<2 weeks	Anorexia, diarrhea, death	Serology for *S.* Pullorum, *S.* Gallinarum

CNS, Central nervous system.

Table 9-59 ■ Antibiotic Treatment of *Salmonella* Infection in Humans and Other Animals

Species	Primary Treatment	Alternative Treatment
Humans (gastroenteritis)	Ciprofloxacin 500 mg PO BID × 5-7 days (14 days if immunocompromised status)[23]	Azithromycin 1 gm PO once, then 500 mg PO q24h × 6 days
Dogs, cats (neonate, geriatric, or debilitated animal)	Follow culture and sensitivity results: trimethoprim-sulfamethoxazole 15 mg/kg PO or SC q12h, chloramphenicol dogs 50 mg/kg PO, IV, IM, or SC q8h; cats 50 mg/kg PO, IV, IM, SC q12h[24] Amoxicillin 10-20 mg/kg PO q8h × 10 days (use trimethoprim-sulfamethoxazole and chloramphenicol with caution in neonates and pregnant animals)	Enrofloxacin 5 mg/kg PO or SC q12h × 7 days[25] (avoid in neonates, pregnant or growing animals)
Cattle, sheep, swine, horses	Septicemia: broad-spectrum antibiotics initially, consider trimethoprim-sulfamethoxazole	Ampicillin, fluoroquinolones, third-generation cephalosporins; check local antimicrobial resistance patterns[19]

of feces, blood, or other localized infections (such as joint fluid or CSF) from ill individuals. Serology is not useful in humans.

In animals, fecal analysis and culture are used to diagnose infection. In poultry, serology is used to identify and eliminate flocks that have carriers of *S. pullorum* and *S. gallinarum*.

Treatment

Treatment in Humans

The mainstay of treatment for enteritis caused by *Salmonella* in immunocompetent adults is fluid and electrolyte replacement. Mild and asymptomatic infection does not require antibiotic treatment. Indications for the use of antibiotics include age younger than 1 year or older than 50 years, compromised immune status, and presence of vascular grafts or prosthetic joints.

When antibiotics are used, their use should be guided by the culture and sensitivity results because some *Salmonella* organisms are resistant to ciprofloxacin and other antibiotics. Evidence of localized infection is an indication for longer courses of treatment. Antimicrobial treatment may also prolong the carrier state, which may affect the ability of some food workers to return to work.

Treatment in Animals

Subclinical carriage in animals is not treated with antibiotics. If an adult dog or cat has uncomplicated gastroenteritis, it also can be treated without antibiotics with isolation, supportive care, and gastrointestinal protectants. Infected neonates, aged, and immunocompromised animals are candidates for isolation, possible plasma transfusions, supportive care, and glucocorticoid (for endotoxic shock) and antibiotic therapy. Fecal cultures should be monitored on a monthly basis to determine whether an animal is a carrier. Table 9-59 shows recommend antibiotics for treatment of *Salmonella* infection in humans and other animals when antibiotic treatment is appropriate.

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SCABIES

Russell W. Currier and Roger I. Ceilley

Sarcoptic itch (ICD-10 B86) Other acariasis (ICD-10 B88.0)

Other names in humans: sarcoptic itch, acariasis, crusted scabies, Norwegian scabies, pseudoscabies, cavalryman's itch, pig-handler's itch

Other names in animals: sarcoptic mange, cutaneous acariasis

Scabies is a skin infestation caused by the mite *Sarcoptes scabiei*. Reports of scabies in humans date back to antiquity, and it was the first infectious disease linked to a specific etiology with the use of a microscope. In 1834 the mite was conclusively demonstrated on a young female patient in a Paris clinic, establishing the association between the mite and its dermatological manifestations.[1] This little-appreciated historical event represented the first etiological diagnosis in medicine. In human medicine, scabies continues to cause both sporadic cases and outbreaks in industrial countries, and immunocompromised persons can experience severe infection. Dogs and many other animals also experience significant infections with variants of *S. scabiei* that are adapted to particular host species. With close contact such as occupational exposure, transmission of animal scabies variants from animals to humans can occur. Although such zoonotic infestations (pseudoscabies) are usually self-limited, they underscore the importance of communication between human and animal health professionals about cases of skin rashes occurring concurrently in humans and animals. This section focuses on scabies, but there are a number of other mite species that infest animals and are capable of causing self-limited skin infections in humans that may be misdiagnosed or missed by medical providers.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Be alert for outbreaks of skin disease caused by scabies in situations of human crowding.
- Consider zoonotic mite infestation as a cause of outbreaks of skin rashes in the community; consult with local veterinarians.
- Educate veterinarians about the zoonotic potential of scabies and other mites and encourage voluntary reporting of cases of sarcoptic mange in animals.

Human Health Clinicians

- Disease usually not reportable but public health authorities should be notified in outbreak settings such as among institutionalized persons and day care centers.
- In evaluating cases of pruritic skin rash, consider possibility of zoonotic transmission of scabies or other mites (pseudoscabies); ask about contact with animals or fomites that could contain mites. Consider consulting a veterinarian.
- Immunocompromised patients may present with heavier scabies mite burdens, requiring extended treatment regimens.
- Delusions of parasitosis can be an underlying condition in the absence of scabies or following diagnosis and treatment of actual infestations.

Veterinary Clinicians

- Counsel owners of a pet with scabies about the risk of human transmission and that it could be self-limiting or persistent, requiring treatment after the pet has been treated.
- Advise health care providers and public health professionals about the risk to humans of animal scabies and other mite infestations.
- Companion animals should be carefully screened for scabies and other mite infestations.
- Animal scabies may be reportable to agriculture/public health authorities if history is linked with a pet store or facility that permits contact with animals in public settings (e.g., petting zoo).
- Some states require reporting of sarcoptic mange in sheep and cattle.

Agent

Sarcoptes scabiei is a species of mite in the family Sarcoptidae that lives parasitically on or in the skin of mammals. Adult mites are 0.3 to 0.5 mm long and roughly circular with four pairs of legs (Figure 9-125). Variants of *S. scabiei* are found in a variety of animal species but are taxonomically
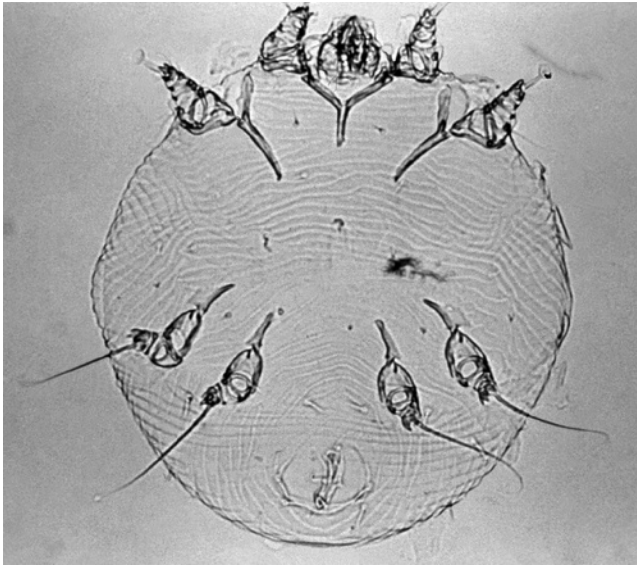
Figure 9-125 ▪ Ventral view of a cleared and mounted *Sarcoptes scabiei* mite. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

Figure 9-126 ▪ Feline scabies. Microscopic image of *Notoedres cati* mite from a skin scraping as seen with a ×10 objective. (From Medleau L, Hnilica KA: *Small animal dermatology: a color atlas and therapeutic guide*, ed 2, St Louis, 2006, Saunders Elsevier. Courtesy G. Norsworthy.)

indistinguishable between human and animal species. For example, scabies in dogs is caused by *S. scabiei* var *canis.*[2] In addition to *S. scabiei*, a number of other mites that infest animals are able to also cause skin rashes in humans. Table 9-60 lists some of these mite species with zoonotic potential.

Dermanyssus gallinae, the red poultry mite, is a nocturnal blood-sucking mite that is the most common mite found in pigeons. Close contact with poultry, wild birds, or nesting material can lead to human infection, which presents as a nonspecific dermatitis that is intensely pruritic and often misdiagnosed.[3,4]

Cheyletiella species, the walking dandruff mite, may be present as a subclinical infection in dogs and cats but can cause an erythematous, papular rash in humans in contact with infected animals. The papules are usually on the arms, trunk, and buttocks and develop into yellow crusted lesions that can be intensely pruritic. Rarely, bullous eruptions and systemic reactions have been reported.[5,6]

Otodectes cynotis is a common mite found in the ears of dogs and cats, where it causes local irritation. It can migrate to other parts of the pet's body, and because it is not host
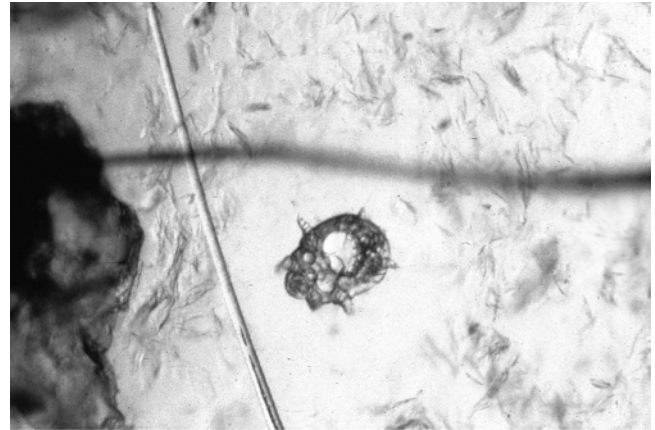
specific, it is capable of infecting humans as well, causing a papular skin rash or an external otitis.[6]

Notoedres cati (feline scabies) is a rare but highly contagious disease of cats that can also infect humans,[7] causing a pruritic rash within hours without visible skin burrows (Figure 9-126 and Color Plate 9-66).

Geographical Occurrence

Scabies is a global problem with widespread distribution in human populations of all ages. It is also found in animal populations worldwide. Outbreaks of often fatal sarcoptic mange in animals have occurred in wildlife populations such as foxes, leading to fluctuations in population size.

Groups at Risk

Human scabies can occur in outbreaks among institutionalized patients[8] or in other situations of crowding such as refugee camps. The presence of immunocompromised patients in such settings may facilitate transmission, and immunocompromised individuals are at risk of more severe infection. Sexual contact is another major risk factor for disease transmission.

Persons at risk for zoonotic transmission of scabies include farmers, veterinarians, wildlife rehabilitators, and pet owners who have close contact with potentially infected animals.

In industrialized nations, scabies often presents as a sexually transmitted parasitic infection with secondary transmission to household members, especially children, who are easily infected when parents or caretakers are infested.[9]

Patients with HIV-AIDS and other immunocompromising states are easily infected and sustain heavy mite burdens leading to crusted or hyperkeratotic scabies.[10]

In animal populations, contact with infected animals is the major risk factor for scabies infection. Puppies, especially those from a pound or animal shelter or whelped in a large breeding kennel, may be at increased risk. Dogs that are allowed to roam freely and contact wildlife or other dogs, including at dog parks, may be at higher risk of infestation.[6]

Table 9-60 ▪ Mites With Zoonotic Potential		
Mite Species	**Name**	**Host Species**
Sarcoptes scabiei	Scabies	Humans, dogs, cattle, foxes, horses, pigs
Dermanyssus gallinae	Red poultry mite	Chickens, pigeons, other birds
Cheyletiella species	Fur mite, walking dandruff mite	Cat, dog, rabbit, small mammals
Otodectes cynotis	Ear mite	Dogs, cats
Notoedres cati	Feline scabies	Cats

Figure 9-127 ■ Hyperkeratosis caused by *Sarcoptes scabiei* in the fox (×22). The mites *(arrows)* are found in the deeper layers of the greatly thickened epidermis. (From Bowman DD: *Georgis' parasitology for veterinarians*, ed 9, St Louis, 2009, Saunders Elsevier.)

Debilitated animals may be at increased risk of severe cases of sarcoptic mange.

Wildlife also can sustain scabies; foxes are particularly susceptible to heavy mite infestations (Figure 9-127). In one case report, a wild red fox *(Vulpes vulpes)* infected a wildlife rehabilitator and a veterinarian who were treating the animal, as well as several dogs residing near a golf course where the affected fox was originally found.[11]

Hosts, Reservoir Species, Vectors

Only one distinct genus and species of *S. scabiei* exists but variants are somewhat host adapted to humans and various specific animal populations. Species affected include dogs, cattle, sheep, pigs, horses, and foxes. Variants adapted to one species may infect another species, but in such instances sustained transmission does not occur.

The *S. scabiei* mite is not considered a vector for other infectious agents, although cases of infestation may become superinfected with *Staphylococcus*, *Streptococcus*, or other bacteria.

Mode of Transmission and Life Cycle

Scabies is transmitted through sustained direct skin-to-skin contact[12] during activities such as sexual contact, holding infants and animals, or while performing hands-on care. Casual contact such as handshaking is unlikely to lead to transmission. Sustained person-to-person and other intraspecies transmission requires adult female mites. After impregnation, the female burrows quickly into the epidermis of the host animal, forming a tunnel in the stratum corneum at the boundary with the stratum granulosum (Figure 9-128). Two to three large eggs are laid daily and these hatch in 4-6 days, giving rise to nymphal mites that molt to adult forms. Eggs develop into adult mites within 10 to 14 days.

Because many variants of the scabies mite cannot live long outside the body, indirect transmission via fomites is generally less important than direct transmission. However, in the case of crusted (hyperkeratotic) scabies, infected individuals have enormous quantities of mites on their person and shed mites on clothing, bed linen, and even furniture.[13] These mites can persist for days on particles of sloughed epidermis. In such situations, contact with fomites can easily lead to further disease transmission.

When an animal strain of *S. scabiei* infects a human, the mite is able to penetrate the skin and rapidly cause a pruritic rash but is unable to successfully reproduce and persist. The result is the self-limited condition termed *pseudoscabies.* Reverse zoonotic transmission can also occur.

Environmental Risk Factors

Mites in the environment are highly susceptible to temperature and humidity conditions and rarely survive beyond 2 to 3 days. Higher ambient temperatures lead to lower survival times.[7] Environmental conditions that predispose human to scabies transmission include crowding and institutionalization. Similarly, environments with animal crowding and
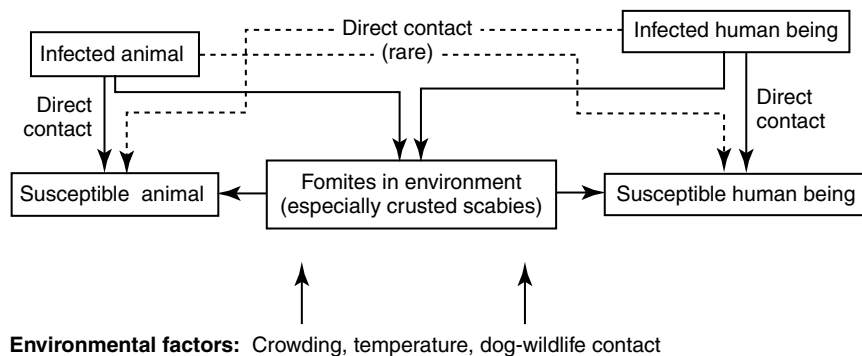

Environmental factors: Crowding, temperature, dog-wildlife contact

Figure 9-128 ■ Scabies transmission.

extensive animal-to-animal contact, such as animal shelters, breeding colonies, dog parks, and crowded kennels, may encourage animal-to-animal transmission of scabies. Areas where wildlife such as foxes contact domestic animals also represent environmental risks.

Disease in Humans

Scabies in humans is manifested about 20 to 35 days after transmission and results in pruritus that is particularly evident in the evening hours while the affected person is trying to sleep. This hypersensitivity is incompletely understood and results from some metabolite of the mites. Skin lesions commonly appear on the webbing of the fingers, genitalia, breasts, flexor surface of the wrists, elbows, and later the abdomen. The burrow or track is diagnostic (Color Plate 9-67) but is not always visible. More commonly papules and vesicles are the most typical skin lesions. Feet and legs are commonly affected areas in children. Rarely do lesions appear on the face and neck except in infants and immunocompromised patients, in whom face and neck lesions are more common.

Elderly patients such as residents of long-term care facilities frequently have extensive lesions on the shoulders and upper back as well as the usual areas noted. Secondary eczematization or thickening of the skin is common in this population, as well as low-grade bacterial infections such as *Staphylococcus aureus* and *Streptococcus pyogenes.* Although these cases are fairly easy to diagnose, they also are more challenging to treat.

Crusted or hyperkeratotic (Norwegian) scabies occurs usually in immunocompromised patients and has a distinctive appearance of grey-green crustiness on the hands and feet, occasionally elbows and arms. Pruritus may be absent. This condition is also easy to diagnose but very difficult to treat. Color Plate 9-68 shows a patient with crusted scabies. In cases of pseudoscabies, intense pruritus and an erythematous rash are often present, but burrows may be absent.

Disease in Animals

The presentation of disease in animals is variable as shown in Table 9-61. The hallmark of animal scabies is pruritus

Table 9-61 ▪ Clinical Presentation of Scabies in Humans and Other Animals

Species	*Sarcoptes scabiei* Variant	Risk Factors	Incubation Period	Clinical Manifestations	Diagnostic Findings
Humans					
Scabies	Variant *hominis*	Crowding	2-6 weeks (1-4 days if previously infested)[18]	Papular rash, vesicles, pruritus	Skin scraping may reveal mites
Crusted scabies	Variant *hominis*	Immunocompromised status, fomites	2-6 weeks[18]	Diffuse crusting lesions, pruritus may be absent	Skin scraping reveals high mite burden
Pseudoscabies (zoonotic)	Animal variants	Direct contact with infected animal	2-6 weeks[18]	Self-limited rash, pruritus	Skin scraping often negative
Dogs	Variant *canis*	Kennels, animal shelters, dog parks, contact with infected wildlife; puppies at increased risk	2-6 weeks[18]	Pruritic papules with thick crusts; abdomen, chest, ears, elbows, and legs affected; alopecia minimal early in disease with more hair loss later	Skin scraping, fecal flotation may reveal mites or eggs; ELISA antibody test can show specific antibodies[7]
Cattle	Variant *bovis*	Rare in United States; contact with infected animals	2-6 weeks[18]	Head, neck, shoulders with later spread to entire body	Skin scrapings showing either mites, eggs, or scybala
Sheep	Variant *ovis*	Rare in United States; contact with infected animals	2-6 weeks[18]	Lesions on nonwooly skin	
Goat	Variant *caprae*	Rare in United States	2-6 weeks[18]	Generalized hyperkeratosis	
Horses	Variant *equi*	Rare in United States; contact with infected animals	2-6 weeks[18]	Intense pruritus Head, neck, shoulders affected; alopecia and crusting; later lichenified with skin folds	
Pigs	Variant *suis*	Contact with infected animals or bedding	2 to 11 weeks	Generalized pruritus; crusting of luminal surface of ears	
Foxes	Variant *vulpes*	Contact with infected animal or bedding	2-6 weeks[18]	Diffuse alopecia, crusting, wasting	

that may not represent location of mites; this is also true for humans (Figures 9-129 and 9-130). Generally longer duration infestations result in thickening of skin with secondary bacterial infections.[7]

In clinical veterinary practice, sarcoptic mange is a common presentation in dogs. The infestation has no age, breed, or sex predilection, occurs with no seasonality, and presents as an intensely pruritic, papular crusting dermatosis affecting the periocular skin, pinnal margins, elbows, and hocks, which may later progress to more generalized involvement, especially of the ventral areas (Figure 9-131). There may be very little to moderate hair loss in contradistinction to demodicosis (eyelash mites) or red mange, which shows little pruritus and extensive alopecia.

In horses, sarcoptic mange is the most severe type of mange, with intensely pruritic lesions on the head, neck, and shoulders. Swine historically have suffered extensive involve-

Figure 9-131 ■ Canine scabies. Generalized alopecia and crusts affecting a pruritic puppy. The alopecic ear pinnae are characteristic of scabies. (From Medleau L, Hnilica KA: *Small animal dermatology: a color atlas and therapeutic guide*, ed 2, St Louis, 2006, Saunders Elsevier.)

Figure 9-129 ■ Sarcoptic mange in a guinea pig caused by *Trixacarus caviae*. (From Quesenberry K, Carpenter JW: *Ferrets, rabbits, and rodents: clinical medicine and surgery*, ed 2, St Louis, 2004, Saunders Elsevier.)

Figure 9-130 ■ Chamois with clinical scabies. The typical lesions begin at the head and neck and then spread over the back. (From Fowler M, Miller RE: *Zoo and wild animal medicine current therapy*, ed 6, St Louis, 2008, Saunders Elsevier. Courtesy T. Steineck, Research Institute of Wildlife Ecology, VMU, Vienna.)

ment, calling for routine mass treatment of most herds. Modern antihelmintic treatment of swine with broad-spectrum parasiticides has successfully eliminated this problem. Foxes may develop severe sarcoptic mange that can be fatal.

Diagnosis

Skin scrapings are the most common and reliable method to demonstrate the presence of mites, eggs, and scybala (discrete fecal pellets) in both humans and other animals. This procedure is as simple as it is essential and could be performed by technicians, nursing staff, physicians, and veterinarians. Standard references[14] call for applying mineral oil (some clinicians prefer to use type B microscopic immersion oil because it is more viscous and easier to work with) to a lesion or placing oil on a sterile scalpel blade (disposable #10 or #20), which is held at a right angle to the skin surface and used to scrape the area in a manner to remove visible skin debris until the superficial skin or stratum corneum is removed, leaving the scraped area pink but not necessarily hemorrhaging. The material adhering to the blade from two to three postage stamp–sized areas is then transferred to a microscope slide, diluted with more oil if necessary, with a cover slip applied after using it to scrape excess oil adhering to the scalpel blade, and the wet mount specimen is examined under ×4 and ×10 low power. The slide should be methodically examined as follows: Sweep left to right, move down one field, and right to left until the entire slide area is examined for mites (adults, nymphs, or larval mites) or distinctive eggs and the smaller scybala (fecal pellets that are numerous and distinct brown-gold/orange in color). Occasionally some skin lesions may be due to the *Demodex folliculorum* mite (eyelash mite) that has widespread distribution in human populations. These distinctive cigar-shaped mites have an elongated tail structure, whereas *Sarcoptes* mites have a distinctive turtle-like shape with four pairs of legs (Figure 9-132).

The scraping procedure not only enables diagnosis within minutes, but also helps to classify patients for mite load. A human patient's scraping with only a mite or two prob-
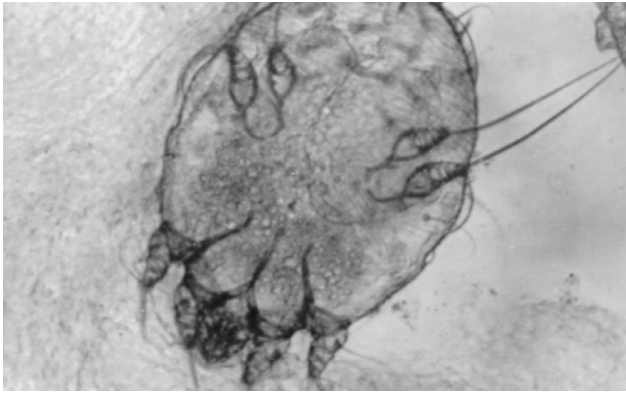
Figure 9-132 ▪ Scabies organism in a wet mount preparation. (From Mandell GL, Bennett JE, Dolin R (eds): *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2005, Churchill Livingstone Elsevier.)

ably is not highly infectious for others (average of 10 adult female mites on a patient) and needs only minimal treatment and simple contact precautions for a brief period of a day or two. However, patients with crusted or hyperkeratotic scabies demonstrate an extraordinary number of mites on each slide. Patients, especially the elderly with a history of extensive home care or long-term care residency, may have a large number of mites from skin with

red, raised, pruritic lesions and evidence of secondary eczematization. Although these lesions are not specifically crusted scabies, these cases are classified as "atypical crusted scabies" or "aggressive scabies" and require more intense treatment and oversight.[15]

In dogs and humans, skin scrapings may not always produce mites or their effects but call for thorough attempts at recovery nonetheless. After scraping and in the absence of mites, a diagnosis can be made based on exclusion of other diseases, epidemiological links, clinical impression (degree of pruritus, history, distribution pattern), and response to treatment.

Other techniques for diagnosis include epidermal shave biopsy, needle biopsy, and burrow ink test. In the latter technique, a blue or black felt-tip pen is rubbed over the lesions and then ink is removed with an alcohol pledget and the blue or black ink dye is pulled into the burrow by capillary action and is diagnostic. A solution of tetracycline can also be applied and examined under a Wood's light.

Treatment

Treatment in Humans

Table 9-62 outlines treatment guidelines with various scabicides. Treatment is preceded with a bath or shower in water

Species	Primary Treatment	Alternative
Table 9-62 ▪ Treatment of Scabies in Humans and Other Animals		
Humans		
Scabies	Permethrin 5% cream, apply entire skin chin to toes, leave on 8-14 hr, repeat in 1 wk (safe in children >2 months)	Ivermectin 200 mcg/kg PO once, second dose after 14 days *or* Crotamiton 10% cream, apply × 24 hr, rinse and reapply × 24 hr[17]
Immunocompromised, crusted (Norwegian) scabies	Permethrin 5% as above day 1, then 6% sulfur in petrolatum daily days 2-7, repeat × several weeks	Ivermectin 200 mcg/kg PO on days 1 and 14 *PLUS* permethrin 5% cream on days 1 and 14[16]
Pseudoscabies (zoonotic mite transmission)	No treatment may be necessary; veterinary consultation for treatment of animal contacts	
Dogs	Lime sulfur dip for young dogs, several dips 5 days apart Selamectin 6 mg/kg topically; repeated twice at 1-month interval[7]	Ivermectin 200 mcg/kg PO or SC, for 2 treatments 2 weeks apart (contraindicated in Collies and Collie crosses)
Cattle	Toxaphene, coumaphos, phosnet, lime sulfur dip (dairy cattle)	Injectable avermectins except dairy cattle
Sheep, Goat	Injectable ivermectin	Doramectin or moxidectin
Horses	Organophosphate insecticide or lime-sulfur solution by spraying, sponging, or dipping; repeat at 12- to 14-day intervals at least 3-4 times[7]	Ivermectin or moxidectin 200 mcg/kg PO × several treatments 2-3 weeks apart
Pigs	Ivermectin 300 mcg/kg SC, repeat in 2 weeks *or* doramectin 300 mcg/kg IM	Lindane, malathion, or chlordane sprays[7]
Foxes	Ivermectin 200 mcg/kg PO or SC, for 2 treatments 2 weeks apart	

of tepid temperature. Patients should clip fingernails and toenails, remove rings and bracelets, and wash the area under nails with a hand brush or toothbrush. Apply the scabicide according to directions behind the ears and from the neck down, paying particular attention to the hands (especially between fingers), the umbilical area, groin, the buttocks, and feet (especially between the toes). The medication should be left on for the prescribed number of hours and then thoroughly rinsed off with tepid soapy water (bath or shower). At the conclusion of therapy, intimate articles of clothing and bed linens should be laundered in hot water and dried on the hot cycle. Patients should be counseled that 24 hours after therapy, they no longer are infectious but may still experience itching for a few weeks afterward. Family members should be treated even if asymptomatic. The majority of patients respond to one treatment, and although there is a lack of well-controlled studies documenting that two applications are better than one, treatment is usually repeated, especially if there is microscopic and/or morphologic evidence of treatment failure. Patients in institutional settings may have a higher mite burden and require one to two additional treatments.

Scabies in immunocompromised individuals (crusted or Norwegian scabies) generally requires much more intense scabicidal treatment. Keratolytic agents (salicylic acid or alpha-hydroxy acid products) can be used to soften tissue, permitting better penetration of topicals, coupled with frequent reassessment and longer periods of contact isolation. Bedding and personal effects initially need special handling. Such patients have heavy mite burdens and need multiple applications of topical treatments.

Treatment of pseudoscabies due to zoonotic mite transmission often relies on treatment of the infected animal and disinfection of the environment. Consultation with a veterinarian is recommended if zoonotic transmission is suspected.

Treatment in Animals

Treatments for animals are summarized in Table 9-62. Requirements vary with species and age of the animal. It is wise to follow label directions owing to risk of toxicity. It is important to counsel animal handlers about risk of human transmission.

Treatment may be approached topically or systemically. Topical treatments include a 2.5% lime sulfur dip (Lym Dip; DVM Pharmaceutical, Inc.) that is licensed for weekly use with a wide margin of safety. Disadvantages include foul odor and staining of light-colored coats. Amitraz (Mitaban; Pharmacia & Upjohn Animal Health) is an alternative and is applied as a 0.025% sponge-on solution at 2-week intervals. Amitraz should not be used on Chihuahuas, in pregnant bitches, or puppies younger than 3 months. Clipping hair of dogs with long coats and/or dense hair coats is recommended. Amitraz vapors can induce hyperglycemia; it should not be

handled by individuals with diabetes or applied to patients with diabetes.

Systemic therapy is an attractive alternative and includes extralabel use of macrocyclic lactones—for example, ivermectin (Ivomec; Merial Animal Health), milbemycin (Interceptor; Novartis Animal Health), moxidectin (Cydectin; Fort Dodge Animal Health), and selamectin (Revolution; Pfizer Animal Health) that are licensed for treatment of canine sarcoptic mange. Ivermectin should not be used in Collies or sheep dogs and their crosses. Consult product literature for safe and proper administration.[16]

It would be prudent to also treat all dogs known to have contact with an affected animal. Concurrent environmental treatment of bedding, grooming equipment, and the general areas of habitation with an ascaricidal spray (e.g., one containing permethrin) is recommended to prevent possible reinfestation.

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TOXOCARA INFESTATION

Peter M. Rabinowitz and Lisa A. Conti

Visceral larva migrans (ICD-10 B83.0)

Other names in humans: roundworm infection, ocular larva migrans, **Toxocara** *infection)*

Other names in animals: roundworm infection, ascariasis

Infection with roundworms of the genus *Toxocara* is probably one of the most common infections associated with ownership of cats and dogs. Puppies and kittens often have symptomatic infections. Visceral or ocular larval migrans can occur in people. Seroprevalence studies suggest 5% to 30% of children may be infected.[1,2]

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide descriptive epidemiology of the likely prevalence in animal and human populations.
- Educate the public on modes of transmission and ways to prevent infection:
  - o Control stray dogs and cats.
  - o Encourage dog and cat owners to have their animals regularly dewormed by a veterinarian.
  - o Encourage basic handwashing awareness.
  - o Discourage keeping raccoons as pets.
  - o Cover sandboxes when not in use.
- Promote local measures to require that dog and cat feces are picked up by owners and do not contaminate local soils and play areas.
- Educate the local veterinary and human health clinicians in risk areas and during high-risk periods about groups at risk and the signs and symptoms of disease.

Human Health Clinicians

- Teach parents, especially pet owners, of the danger of contamination and exposure of areas by feces from untreated dogs and cats.
- Teach parents to not allow geophagia.
- Teach patients to always wash hands after handling soil and before eating.[3]
- Encourage patients with dogs and cats to ensure adequate veterinary treatment for worm infection. It is especially important for pregnant dogs and cats and young puppies and kittens to be dewormed. If a human health clinician inquires about this, it might raise awareness.
- No human vaccine is available.

Veterinary Clinicians

- Ensure pet owners bring animals for strategic deworming and prompt parasite treatment.

- Counsel pet owners about the proper disposal of animal feces and handwashing.
- See the CDC manual about toxocariasis for veterinarians that reviews specific prevention and treatment measures[4]; available online at http://www.cdc.gov/ncidod/dpd/parasites/ascaris/prevention.htm.
- Recommend keeping cats indoors.

Agent

Toxocara canis and *T. cati* are ascarid roundworms (nematodes) that are large (10 to 12 cm long) and live in the small intestine of carnivorous mammals but also migrate into tissues and cause extraintestinal pathology (Figure 9-133). *T. canis* is recognized more widely in both animals and humans than *T. cati*
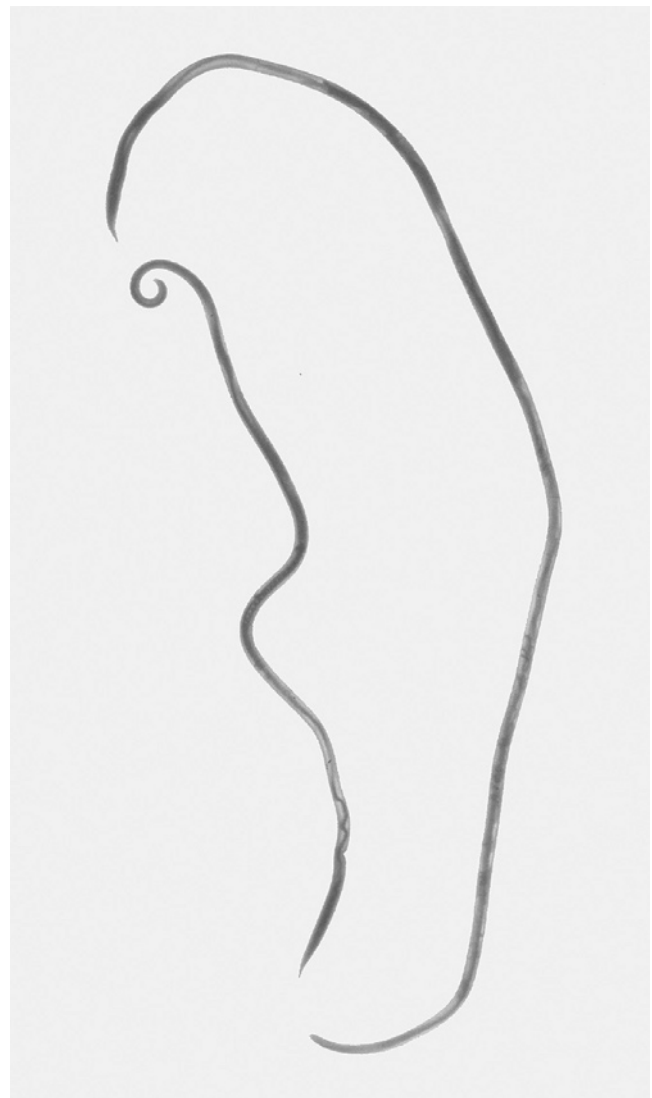

Figure 9-133 ▪ Adults of *Toxocara canis*. The male measures 6 cm and the female measures 9 cm in length. (From Long SS, Pickering LK, Prober CG: *Principles and practice of pediatric infectious diseases*, ed 3, Edinburgh, 2008, Churchill Livingstone Elsevier.)

and causes more serious infections in dogs.[5] *Toxascaris leonina* is seen in adult dogs and cats and is less well recognized as a zoonotic agent. The raccoon roundworm, *Baylisascaris procyonis*, results in rare but serious disease in humans.

Geographical Occurrence

Toxocara infections occur worldwide, with human seroprevalence rates varying widely (from 0 to more than 80%) among populations.[3] A recent CDC study estimated the seroprevalence rate in the United States at 14%.[6] In one study, more than 30% of dogs younger than 6 months sampled across the United States were shedding *T. canis* eggs, whereas rates of feline infection with *T. cati* have been reported to exceed 25%.

Groups at Risk

Although roundworms can occur in adults, disease in children is most frequently reported. A recent CDC seroprevalence study found increased risk among children and youth younger than 20 years. Children are believed to have the highest attack rates as a result of direct contact with dogs and cats and/or soil contaminated by infective eggs. Children with pica (inappropriate ingestion of soil and other substances related to nutritional deficiencies) are considered at increased risk.

Hosts, Reservoir Species, Vectors

Humans, dogs, cats, and wild carnivores can develop clinical manifestations. Humans are a terminal host, meaning that the roundworms cannot reproduce and carry on their life cycle. Rodents are paratenic hosts.[7]

Mode of Transmission and Life Cycle

In both animals and humans, infection often begins by swallowing of infective, embryonated eggs. Because the eggs take up to two weeks to embryonate, the source of eggs is usually contaminated soil or food rather than direct contact with an infected animal.[8] These eggs then hatch, the larvae penetrate the intestinal mucosa, and then migrate through the liver and bloodstream to the lungs (Figure 9-134). In humans,
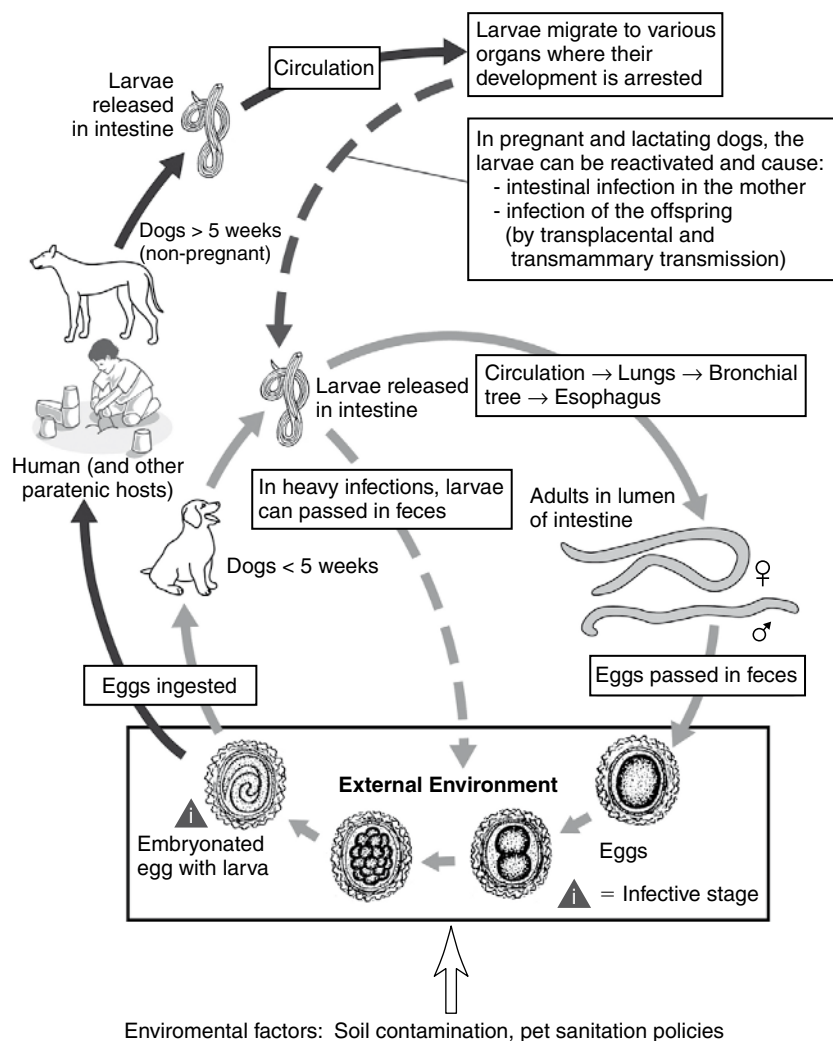

Figure 9-134 ■ Life cycle of *Toxocara canis* and *Toxocara cati*, the causal agents of toxocariasis. (Adapted from Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

they may then pass to other tissues as well, causing granulomatous lesions in the lungs and abdominal organs (visceral larva migrans) or the eye (ocular larva migrans).[3] If infective eggs are swallowed by a puppy, the larvae hatch and migrate as above; but once in the lungs, the larvae are often coughed up and swallowed to then mature into adult worms in the animal's small intestine. These adult worms then produce eggs, which are shed in the puppy's feces, and also can cause abdominal distention and obstruction.

Transplacental transmission occurs when a pregnant bitch transmits infective larvae directly to the developing fetus. Larvae that migrate to the mammary gland can also be passed to puppies during nursing.[5]

Cats are thought to be infected by eating tissue containing larvae of other infected animals, especially rodents.[7] Transplacental passage of *T. canis* is not thought to occur in cats, but transmammary transmission has been reported.[4]

Environmental Risk Factors

Because the eggs of *Toxocara* species can survive for years in soils,[7] the degree of environmental contamination of playgrounds, sandboxes, and other locations frequented by children is a significant environmental risk factor. In surveys in the United States, the United Kingdom, and Japan, 30% of playground soil samples and 75% of sampled sandboxes contained potentially infectious eggs.[3]

Disease in Humans

Toxocara infection in humans is usually asymptomatic. When disease develops, it is often chronic and mild and related to hypersensitivity response to larval invasion of tissues. The two main forms of disease are visceral larva migrans and ocular larva migrans.

Visceral larva migrans is seen particularly among preschool children. Signs and symptoms include fever, weight loss, wheezing, cough, abdominal pain, skin rashes, and hepatosplenomegaly. Laboratory findings include leukocytosis and eosinophilia.

Ocular larva migrans may develop as long as 10 years after infection with *T. canis* and is usually seen among older children who present with unilateral vision loss. Findings on examination can include a subretinal mass, leukocoria, cataracts, and retinal scarring (Color Plate 9-69).[8] When motile larvae are trapped in the eye, a diffuse unilateral subacute neuroretinitis can occur.[9]

Disease in Animals

T. canis infection in dogs usually produces more severe signs in puppies than in older dogs. In puppies infected in utero, a parasitic pneumonia may develop with a resultant high mortality rate. Development of a large parasitic load in the intestine may lead to abdominal distention, colic, anorexia, vomiting, rough hair coat, diarrhea, cachexia, coughing, and sometimes death. Neurological involvement may occur including twitching and seizures. Eosinophilia is often seen.

Cats generally have less severe disease than dogs. A potbellied appearance, diarrhea, and vomiting may develop. Eosinophilia is common.[7]

Table 9-63 compares the clinical presentations of toxocariasis in humans and other animals.

Diagnosis

In humans, clues to the diagnosis of visceral larva migrans include a history of exposure to contaminated soils or foods, the appearance of typical signs and symptoms, eosinophilia,

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Table 9-63 ▪ Toxocariasis: Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans: visceral larva migrans	Preschool age: ingestion of contaminated soils or food	Weeks to months (the disease is self-limited but the larvae may remain dormant in tissues for years)	Abdominal pain, fever, hepatosplenomegaly, rash, wheezing	Leukocytosis, eosinophilia, anti-*Toxocara* antibodies
Humans: ocular larva migrans	Children	Up to 10 years	Unilateral vision loss, retinal scarring/ subretinal mass on examination	
Dogs (usually *Toxocara canis*)	Prenatal exposure, nursing, ingestion of contaminated soils	Weeks	Parasitic pneumonia, respiratory difficulty, death Abdominal infection: abdominal distention, vomiting, diarrhea	Eosinophilia, leukocytosis, eggs in feces
Cats (usually *T. cati*)	Ingestion of soils containing eggs, nursing or eating animal tissue containing larvae	Weeks	Abdominal distention, vomiting, diarrhea	Eosinophilia, leukocytosis, eggs in feces

and antibodies to *Toxocara*. Enzyme immunoassay with *Toxocara* excretory-secretory antigens is the preferred serological test.[8] However, it may lead to underdiagnosis if a person is infected with an unusual serovar not well covered by the standard test. Serial serology titers are required to document seroconversion; a fourfold increase in titer is considered evidence of recent infection.[10]

Ocular migrans is diagnosed clinically. Antibody titers to *Toxocara* species may be elevated in aqueous and vitreous fluid compared with serum levels, which may aid in diagnosis. The differential diagnosis includes other causes of retinal masses, including retinoblastoma.[9]

In animals, the detection of eggs in feces through a fecal flotation test is diagnostic (Figure 9-135). The spherical, pitted eggs of *T. canis* and *T. cati* can be distinguished from the smooth, ovoid eggs of *T. leonine,* which has less zoonotic potential.[5]
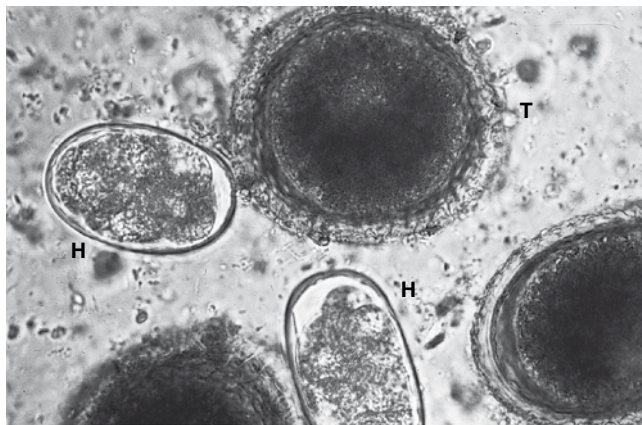

Figure 9-135 ■ Photomicrograph of a fecal flotation analysis from a dog demonstrating characteristic ova from hookworms *(H)* and *Toxocara canis (T)*. (Magnification ×400.) (From Willard MD: Disorders of the intestinal tract. In Nelson RW, Couto CG (eds): *Small animal internal medicine*, ed 4, St Louis, 2009, Mosby Elsevier. Courtesy Tom Craig, Texas A & M University.)

Treatment

Treatment in Humans

Antihelmintic treatment is directed toward relief of symptoms. Because infection is generally asymptomatic in humans, treatment is sometimes withheld. In cases of severe organ involvement, steroids may be indicated in addition to antihelmintics. Table 9-64 outlines treatment guidelines in humans and other animals.

Treatment in Animals

In dogs and cats, infection is usually treated aggressively with a number of antihelmintic agents. Because transplacental infection does not occur with *T. cati*, cats are usually treated as kittens.

Strategic deworming against roundworms (and hookworms) includes deworming the pregnant dog; treating puppies and kittens beginning at 2 weeks of age, then every 2 weeks through weaning (6 to 8 weeks); and then treating monthly until the pet is 6 months old. Nursing dogs and queens should be treated with their litters. Older animals can be monitored through at least annual fecal examinations. Many pups and kittens are not brought to the veterinarian until they are 6 to 8 weeks, so owners of pregnant animals need to work with their veterinarians to ensure earlier deworming.

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Table 9-64 ■ Toxocariasis Treatment in Humans and Other Animals		
Species	**Primary Treatment**	**Alternative**
Humans: visceral larva migrans	Albendazole 400 mg PO BID × 5 days	Mebendazole 100-200 mg PO bid × 5 days[11]
Humans: ocular migrans	First 4 weeks of symptoms: prednisone 30-60 mg PO qd, *PLUS* subtenon triamcinolone 40 mg/week × 2 weeks[11]	
Dogs: treatment in pregnancy	Fenbendazole 50 mg/kg PO q24h from day 40 of gestation to 2 weeks after birth Milbemycin oxime 0.5 mg/kg PO Pyrantel pamoate 5-10 mg/kg PO	Ivermectin 1 mg/kg PO q24 on days 20 and 42, or 0.5 mg/kg PO on days 38, 41, 44, and 47[7]
Dogs: pups at 2 weeks of age then every 2 weeks until 8 weeks, then monthly thereafter	Pyrantel pamoate 5 mg/kg PO Fenbendazole 50 mg/kg PO q24h × 3 days Milbemycin oxime 0.5 mg/kg PO	Praziquantel/pyrantel/febantel (praziquantel 5-12 mg/kg) PO once
Cats	Fenbendazole 50 mg/kg PO q24h × 3 days Pyrantel pamoate 5 mg/kg PO	Selamectin 6/mg/kg topically

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TOXOPLASMOSIS

Peter M. Rabinowitz and Lisa A. Conti

Toxoplasmosis (ICD-10 B58) Congenital toxoplasmosis (P37.1)

Other names in humans: *Toxoplasma* infection

Other names in animals: *Toxoplasma* infection

Toxoplasmosis is a common zoonotic infection in nearly all mammals and some birds caused by the obligate, intracellular organism *Toxoplasma gondii*. Cats are the definitive host, shedding oocysts in their feces. Toxoplasmosis can cause severe and fatal disease in fetuses and immunocompromised patients. Ingestion of oocysts following contact with cat feces or contaminated soil is a pathway for human infection. However, a number of human infections are believed to result from eating raw or undercooked meat containing infectious cysts.[1] Toxoplasmosis is a disease that underscores the importance of communication between veterinarians and human health clinicians; studies have found that many physicians provide inappropriate advice to their pregnant patients regarding the risk of disease from cats.

Figure 9-136 ▪ A pregnant woman in the process of washing a batch of assorted produce before the preparation of a salad. Note that the food preparation area around the sink is also kept clean and free of unclean kitchen implements either inside or outside the sink. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy James Gathany.)

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Educate the public on reducing risk of infection by:
  - Proper food handling (fruits and vegetables thoroughly washed or peeled) and cooking (145° F for beef or lamb; 160° F for pork, ground meat, or wild game; 180° F for poultry).
  - Appropriate kitchen hygiene (washing items in hot soapy water after they come in contact with raw meats or unwashed fruits and vegetables) (Figure 9-136).
  - Appropriate hand hygiene: washing hands after handling raw meats, soil, or sand.
  - Pregnant women and immunocompromised persons should wear gloves when handling soil, sand, and avoid handling soil. They should avoid handling cat feces by having someone else change the cat litter or by wearing gloves to do so. They should not have to give up their cat (Figure 9-137).
  - Keeping sandboxes covered and vegetable gardens fenced.

- Educate local veterinary and human health clinicians about the signs and symptoms of the disease.
- Work with local animal control agencies to encourage control of stray cat populations.

Human Health Clinicians

- Educate patients (particularly seronegative pregnant patients and immunocompromised patients) about risk reduction (avoidance). With such measures, pregnant and immunocompromised individuals should not have to give up a cat.
- No human vaccine is available.

Veterinary Clinicians

- Counsel pet owners about the following additional preventive steps:
  - Do not feed bones, viscera, unpasteurized milk (especially goat's milk), or raw or undercooked meat to cats.
  - Wash your hands after handling cats and cat litter.
  - Dispose of cat litter on a daily basis to reduce the risk of exposure to infectious oocysts.
  - Disinfect cat litter box with boiling water on a weekly basis.
  - Keep cats indoors.

Figure 9-137 ■ A pregnant woman is about to pet her cat while her husband is in the process of changing the cat's litter so that the woman can avoid contact with possible pathogens such as *Toxoplasma gondii*, the etiologic agent responsible for the disease toxoplasmosis. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy James Gathany.)

- Counsel owners that healthy seropositive cats are little danger to owners. Seronegative cats that have the potential to become infected and shed oocysts are more of a human risk.
- A modified live vaccine is available in Europe and New Zealand for sheep.

Agent

Toxoplasma gondii is a protozoan that has three infectious stages: oocysts (shed in the feces, containing sporozoites), tachyzoites (rapidly multiplying form found in tissues), and bradyzoites (slowly multiplying form found in tissues; Figure 9-138).[2] In addition, tissue cysts (found in muscle or CNS tissue) contain dormant bradyzoites.

Geographical Occurrence

The disease is found worldwide. The U.S. National Health and Nutrition Examination Survey (NHANES 1999-2004) found an age-adjusted *T. gondii* seroprevalence among persons 6 to 49 years old of 10.8% (95% confidence limits [CL] 9.6%, 11.9%), and a rate among women of childbearing age (15 to 44 years) of
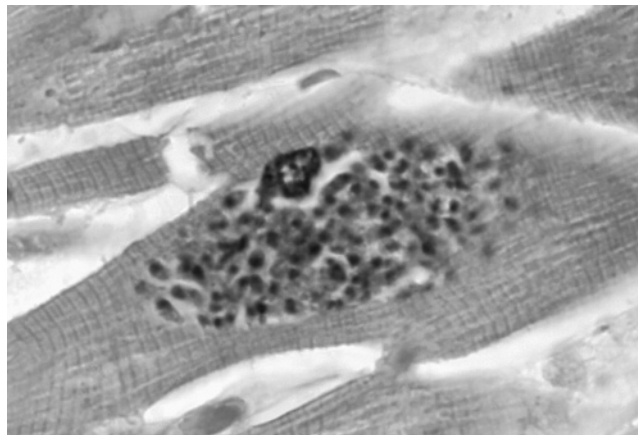

Figure 9-138 ■ Histopathology of active toxoplasmosis of myocardium. Numerous tachyzoites of *Toxoplasma gondii* are visible within a pseudocyst in a myocyte. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Edwin P. Ewing, Jr.)

11.0% (95% CL 9.5%, 12.4%).[3] Higher rates have been reported in other parts of the world, including European countries where undercooked meat consumption is common, and sub-Saharan Africa where extensive contact with cats can occur.[1]

Groups at Risk

Analysis of NHANES data has suggested that individuals in occupations with soil contact, lower educational level, living in crowded conditions, and foreign-born individuals are at increased risk.[1] Other studies have reported increased risk with cat ownership, soil contact, eating unwashed vegetables, and eating undercooked or raw meat. In a number of studies, however, current ownership of a cat has not been associated with increased risk of seropositivity.[1] Fetuses and immunocompromised persons are particularly vulnerable to severe sequelae from infection.

Hosts, Reservoir Species, Vectors

Cats and other felids are the only hosts in which *T. gondii* can reproduce sexually. Infection is most commonly seen in intermediate hosts such as humans, sheep, goats, swine, dogs, and horses, although most mammals and some birds are infected. Game animals such as deer can be infected with tissue cysts, posing a risk for human consumption.

Mechanical vectors include contaminated vegetables and other food products, soil, and sand.

Mode of Transmission and Life Cycle

When naïve cats ingest viable *Toxoplasma* organisms, the parasite is able to reproduce in the cat's intestinal lining and results in the shedding of immature oocysts in the feces. After a period of 2 to 3 weeks, the cat develops immunity and no longer sheds oocysts. The immature oocysts shed in cat feces are not immediately infectious but take 1 to 5 days to sporulate into mature oocysts with viable sporozoites (Figure 9-139). These infectious oocysts can persist in the environment for

Toxoplasmosis
(*Toxoplasma gondii*)

Both oocysts and tissue cysts transform into tachyzoites shortly after ingestion. Tachyzoites localize in neural and muscle tissue and develop into tissue cyst bradyzoites. If a pregnant woman becomes infected, tachyzoites can infect the fetus via the bloodstream.

▲ = Infective Stage
▲ = Diagnostic Stage

Serum, CSF

▲ Diagnostic Stage
1) Serological diagnosis.
or
2) Direct identification of the parasite from peripheral blood, amniotic fluid, or in tissue sections.
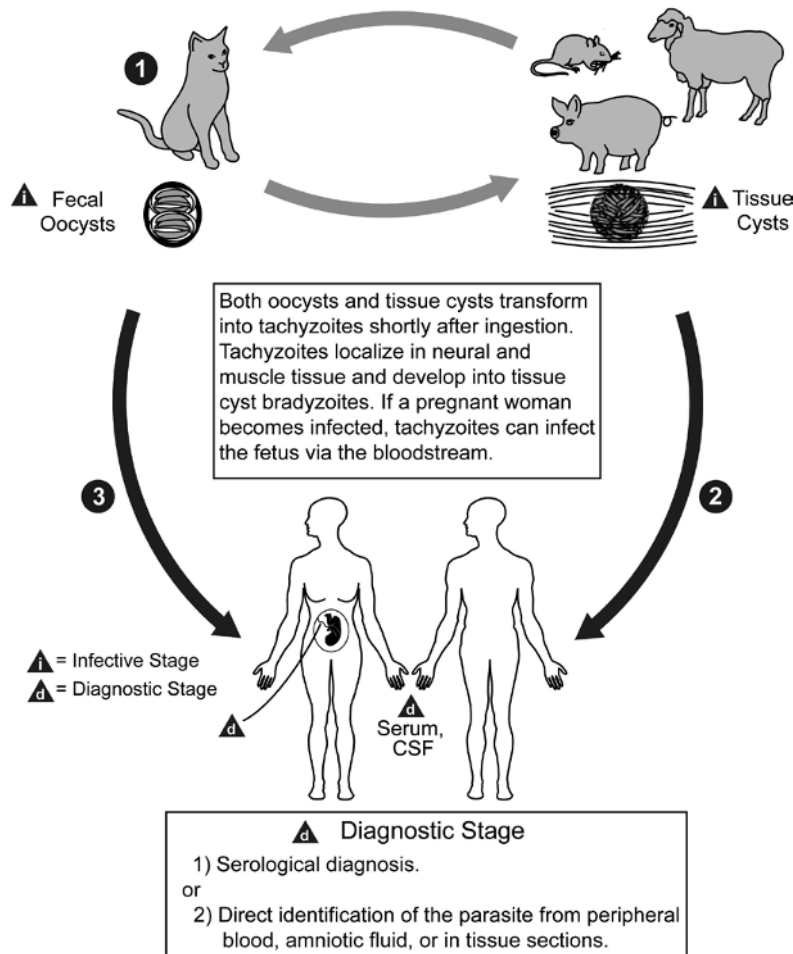
Figure 9-139 ▪ Life cycle of toxoplasmosis. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Alexander J. DaSilva and Melanie Mosher.)

several months. If they are ingested by an intermediate host either directly or through contaminated soil, they begin to asexually multiply in the host's intestinal epithelium and produce tachyzoites. The tachyzoites disseminate in the intermediate host's bloodstream and lymph system both freely and intracellularly within monocytes and macrophages.[4] After several weeks of rapid multiplication, the intermediate host may develop immunity. Once the host is immune, the life cycle shifts to the production of bradyzoites, which multiply less rapidly and tend to form tissue cysts in brain, myocardial, and nervous tissue where they may persist for life.

If an intermediate host ingests raw or undercooked meat containing these cysts, the bradyzoites may be released and develop into tachyzoites. The first time cats are infected, the parasite's life cycle is completed when some of the bradyzoites initiate a sexual cycle to produce unsporulated oocysts that are shed in the feces for 1 to 2 weeks. Cats are typically resistant to reinfection.[5]

The primary routes of toxoplasmosis transmission to humans are the ingestion of raw or undercooked meat that contains viable cysts, the ingestion of infectious oocysts due to contact with cat feces or contaminated soil or fomites, and congenital infection. The relative importance of these different routes of transmission is poorly understood and probably varies by geographical region. A survey of more than 6000 commercial samples of beef, chicken, and pork from retail stores in the United States found a low incidence of infectious cysts, with viable *T. gondii* detected only in samples of pork.[6] Transplacental transmission occurs during active infection of the mother with the tachyzoite phase. The risk of transmission from an infected pregnant woman to her fetus is considered lower in early pregnancy (although the consequences to the fetus are greater) than in subsequent weeks.[7] Other transmission pathways include organ transplants and blood transfusions.

Environmental Risk Factors

A number of factors, such as humidity and temperature, determine how long it takes for immature oocysts to develop into mature infectious oocysts and how long such oocysts can persist in soil and water and on environmental surfaces.

Disease in Humans

Most cases of toxoplasmosis in immunocompetent children and adults are asymptomatic. Symptoms, when they occur, are usually self-limited and can include significant cervical or other lymphadenopathy and fever with atypical lymphocytosis. Rarer complications can include toxoplasmic chorioretinitis, myocarditis, and myositis. The incidence of ocular toxoplasmosis in immunocompetent persons is believed to be more common than previously thought, and toxoplasmosis is one of the most common causes of uveitis in the general population, leading to vision loss in some cases.[8,9] Encephalitis and even death can occur but are rare in immunocompetent hosts.[9]

In immunocompromised patients, toxoplasmosis often produces severe disease, including encephalitis and cerebral abscesses (Figure 9-140), pneumonitis, chorioretinitis (Color Plate 9-70), and myocarditis with a high mortality rate if the disease is not treated in a timely fashion. Symptoms of encephalitis can include confusion, seizures, sensorimotor deficits, and ataxia.[10] Infection in immunocompromised humans may be the result of reactivation of latent infection but can also result from acute infection. Organ transplants can be a source of infection in immunocompromised persons.[9]

One of the most significant complications of human toxoplasmosis infection occurs when a pregnant woman is in the acute phase of the illness (tachyzoite phase) and the organism passes to a fetus, resulting in congenital infection. Congenital toxoplasmosis can present as mild to severe disease, with complications including hydrops fetalis, perinatal death, prematurity, decreased birth weight, retinal scarring, and a classical triad of chorioretinitis, hydrocephalus, and cerebral calcifications (Figure 9-141). Although more than half of infected newborns are considered normal shortly after birth, most will develop ocular and/or other complications if not treated.[11]

Disease in Animals

Evidence of past infections in cats and many other animal species is common, but clinical cases are rarely recognized because most infections are subclinical (Figure 9-142). In cats, the disease is most commonly seen in congenitally infected kittens, leading to stillbirth, neonatal fever, respiratory distress, uveitis, and neurological involvement (Color Plate 9-71).[12] It is also seen in immunocompromised animals with lethargy, fever, neurological signs, or generalized retinitis (Color Plate 9-72).

Dogs, especially puppies, may develop acute signs of infection including fever, respiratory signs (Color Plate 9-73), and diarrhea. Immunosuppressed older dogs may manifest neurological involvement (Figure 9-143).

In sheep, goats, and swine, toxoplasmosis can cause abortion and neonatal mortality (Figure 9-144). Birds, including poultry, are commonly infected but generally do not manifest clinical signs. Table 9-65 compares clinical presentations of toxoplasmosis in humans and other animals.
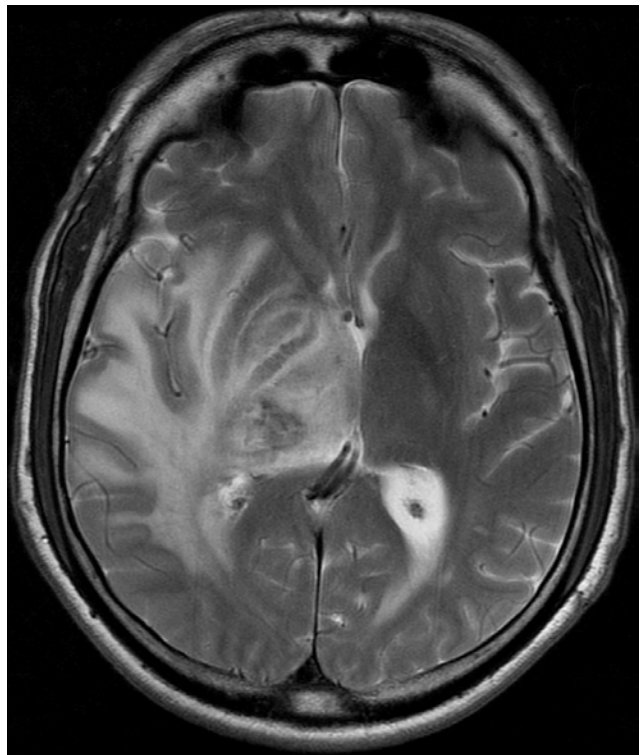
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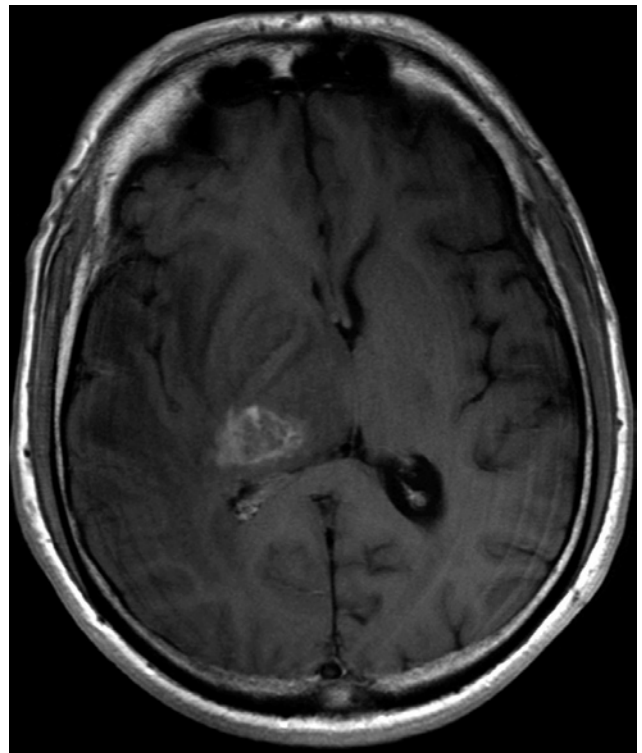
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Figure 9-140 ■ MRI images of *Toxoplasma* abscess in the right thalamus with extensive surrounding vasogenic edema and irregular peripheral enhancement. **A**, Axial T_2-weighted and (**B**) gadolinium-enhanced T_1-weighted images. (From Adam A, Dixon AK (eds): *Grainger & Allison's diagnostic radiology*, ed 5, Edinburgh, 2008, Churchill Livingstone Elsevier.)

Figure 9-141 ▪ Congenital toxoplasmosis with hydrocephalus. (Courtesy Peter Rabinowitz.)
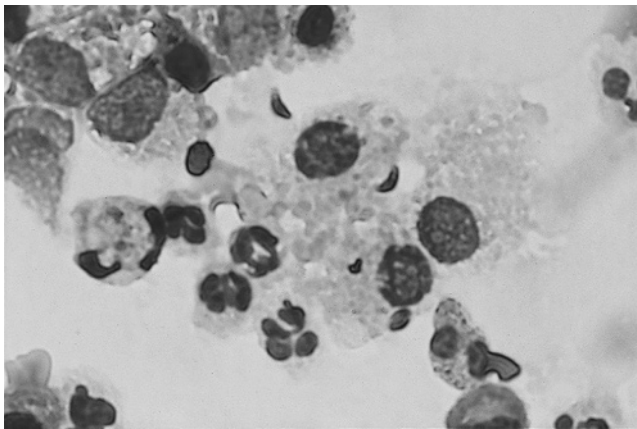

Figure 9-142 ▪ Photomicrograph of *Toxoplasma gondii* tachyzoites from the lungs of a cat with acute toxoplasmosis. The extracellular tachyzoites are crescent shaped with a centrally placed nucleus. They are approximately 6 microns in length (bronchoalveolar lavage fluid, Wright stain). (From Hawkins EC: Diagnostic tests for the lower respiratory tract. In Nelson RW, Couto CG (eds): *Small animal internal medicine*, ed 4, St Louis, 2009, Mosby Elsevier.)

Diagnosis

In humans, the cornerstone of diagnosis is serology.[13] High titer of anti-*Toxoplasma* IgM suggests an acute infection (IgM titers can persist for 18 months), whereas IgG antibodies may indicate past infection. Elevated IgM titers can be verified at a *Toxoplasma* reference laboratory such as the CDC or Toxoplasmosis Serology Lab (Palo Alto Medical Foundation Research Institute).[5] When congenital toxoplasmosis is suspected, diagnostic studies include maternal seroconversion detected via the immunosorbent agglutination assay (ISAGA), fetal ultrasound findings, and amniocentesis with PCR detection of *T. gondii.*

In animals, the serological testing for IgG, IgM, and antigen with follow-up tests in 3 weeks helps differentiate acute from chronic infection. The IgM antibodies rise 2 weeks after infection and may persist for a maximum of 3 months. A fourfold increase in IgG titers between samples is also suggestive of a recent infection.[12]
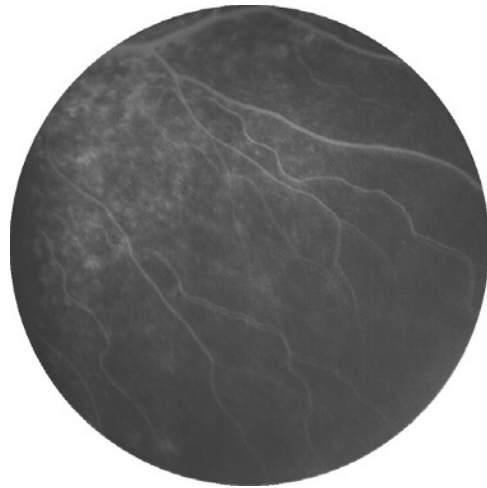

Figure 9-143 ▪ Lipemia retinalis in a Dachshund with toxoplasmosis. Lipemia retinalis makes blood vessels look pink (red blood with white lipid added). There are multifocal gray opacities indicative of active chorioretinitis. (From Dziezyc J, Millichamp NJ: *Color atlas of canine and feline ophthalmology*, St Louis, 2005, Saunders Elsevier.)
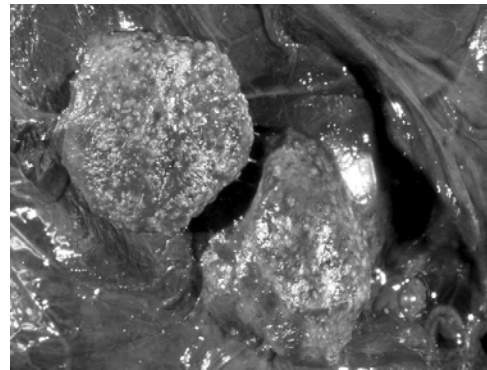

Figure 9-144 ▪ Ovine protozoal placentitis, toxoplasmosis, abortion, placenta, sheep. The cotyledons have hundreds of white foci of necrosis, a lesion that is characteristic of *Toxoplasma gondii*–induced abortion in sheep and goats. (From McGavin MD, Zachary JF: *Pathologic basis of veterinary disease*, ed 4, St Louis, 2007, Mosby Elsevier. Courtesy Ontario Veterinary College, University of Guelph.)

Treatment

Treatment in immunocompetent humans is usually not indicated because of the mild and self-limited nature of the disease. If significant organ involvement occurs or in particular clinical situations such as immunocompromise, pregnancy, and congenital infection, antimicrobial treatment is necessary (Table 9-66). In addition to antimicrobials, prednisone is added to the treatment regimens for congenital toxoplasmosis, chorioretinitis, and toxoplasma meningitis. The recommended treatment regimens are complex, and consultation with an infectious disease specialist is advisable.

Antibiotics can be used in animals but they may not clear infection.

Table 9-65 ■ Toxoplasmosis: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Human beings		10-23 days		
Immunocompetent	Ingestion of raw or undercooked meat or direct exposure to oocysts from cat feces		Usually asymptomatic in immunocompetent host, or lymphadenopathy, chorioretinitis can occur	Immunohistochemical staining, PCR, serology (IFA, ELISA)
Immunocompromised	Reactivation of latent disease or new infection (see above), organ transplants		Encephalitis, pneumonitis, chorioretinitis, other	Abnormal CT, MRI, CSF findings
Congenital	Maternal infection		Fetal death, prematurity; triad of chorioretinitis, hydrocephalus, cerebral calcifications; delayed ocular disease	Maternal seroconversion detected via ISAGA; fetal ultrasound findings, amniocentesis with PCR detection of *Toxoplasma gondii*
Cats	Hunting, immunodeficiency, congenital	3-21 days	Usually subclinical Neurological involvement Fever, respiratory distress, ocular involvement	Serology (ELISA, IFA, CF), fecal flotation for active infection (oocysts are 10-12 mcm)
Dogs	Ingestion of undercooked meat, immunodeficiency, congenital	Weeks	Usually subclinical, varies with organ system involvement, including encephalitis, myositis, hepatitis, and retinitis	As with cats
Sheep, goats	Ingestion of oocysts from contaminated soil	Weeks	Abortion, neonatal death	As with cats

CF, Complement fixation; *CSF*, cerebrospinal fluid; *CT*, computed tomography, *ISAGA*, immunosorbent agglutination assay; *MRI*, magnetic resonance imaging.

Table 9-66 ■ Toxoplasmosis Treatment in Humans[14] and Other Animals[15]

Species	Primary Treatment	Alternative
Humans: Immunocompetent		
Acute illness with lymphadenopathy	No treatment unless severe symptoms or significant organ involvement	
Active chorioretinitis, meningitis, transfusion related	Pyrimethamine 200 mg PO on day 1, then 50-75 mg q24h *PLUS* sulfadiazine 1-1.5 gm PO qid *PLUS* leukovorin (folinic acid) 5-20 mg 3×/wk, treat 1-2 week beyond resolution of signs/symptoms; continue leukovorin 1 week after stopping pyrimethamine, *PLUS* prednisone 1 mg/kg/day in 2 divided doses for acute inflammation[16]	
Acute infection in pregnancy	*<18 wk gestation:* spiramycin 1 gm PO q8h until delivery if amniotic fluid PCR negative *>18 wk gestation and documented infection:* pyramethamine 50 mg PO q12h x 2 days then 50 mg/day *PLUS* sulfadiazine 75 mg/kg PO x 1 dose then 50 mg/kg q12h (max. 4 gm/day) *PLUS* folinic acid 10-21 mg PO daily	
Congenital	Management complex; consultation with specialist advisable; pyrimethamine *PLUS* sulfadiazine *PLUS* leucovorin[16]	
Patients With AIDS		
Cerebral toxoplasmosis	Pyrimethamine 200 mg PO, then 75 mg/day PO *PLUS* sulfadiazine 1-1.5 gm PO qd *PLUS* folinic acid 10-20 mg/day PO × 4-6 weeks after signs/symptoms resolve; then suppressive treatment *or* TMP-SMX 10/50 mg/kg/day PO/IV divided q12h × 30 days	Pyrimethamine PLUS folinic acid PLUS either clindamycin, clarithromycin, azithromycin, or atovaquone[16]
Suppression after treatment of cerebral toxoplasmosis	Sulfadiazine 500-1000 mg PO 4×/day *PLUS* pyrimethamine 25-50 mg PO q24h *PLUS* folinic acid 10-25 mg PO q24h	Clindamycin *PLUS* pyrimethamine *PLUS* folinic acid *or* atovaquone[16]
Primary prophylaxis: patients with AIDS with CD4 <100 and positive IgG *Toxoplasma* antibody	TMP-SMX DS 1 tab PO q24h *or* TMP-SMX-SS 1 tab PO q24h	Dapsone *PLUS* pyrimethamine *PLUS* folinic acid *or* atovaquone[16]
Cats	Clindamycin 10-12.5 mg/kg PO/IM q12h × 2-4 wk	Trimethoprim-sulfadiazine 15 mg/kg PO/IV q12h × 2 wk
Dogs (Rare)	Clindamycin 10-12.5 mg/kg PO/IM q12h × 2-4 wk	Trimethoprim-sulfadiazine 15 mg/kg PO/IV q12h × 2 wk[13]

TMP-SMX, Trimethoprim-sulfamethoxazole.

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

Peter M. Rabinowitz and Lisa A. Conti

Subacute spongiform encephalopathy, Creutzfeldt-Jakob disease (CJD) (ICD-10 A81.0)

Other names in humans: variant CJD, fatal familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker disease (GSS), prion disease, TSE, kuru

Other names in animals: bovine spongiform encephalopathy (BSE), mad cow disease, feline spongiform encephalopathy (FSE), chronic wasting disease of elk and deer (CWD), transmissible mink encephalopathy (TME), exotic ungulate encephalopathy, scrapie

In 1986, an outbreak of bovine spongiform encephalopathy (BSE) occurred in the United Kingdom that was eventually linked to the use of livestock feed containing meat and bone from animals infected with a prion disease (*prion* is short for *proteinaceous infectious particle*). Shortly afterward, outbreaks of transmissible spongiform encephalopathies (TSEs) were reported in zoo animals and domestic cats that had consumed BSE-contaminated meat products. In retrospect, this unusual occurrence of prion diseases in animals was a sentinel event for human health risk. In 1996, the emergence in humans of a variant form of Creutzfeldt-Jakob disease (vCJD), a progressive dementia, was attributed to consumption of contaminated beef from BSE-infected cattle. As a result of the implementation of a number of feed bans, such as a prohibition against feeding mammalian protein to any farmed animals in the United Kingdom, the incidence of reported cases of both BSE and vCJD has dropped dramatically in recent years. Outbreaks in cats and other animals also declined related to similar feed bans.

Despite the success in controlling BSE and vCJD, prion diseases continue to be a public health concern. Sporadic Creutzfeldt-Jakob disease (CJD), which has no known link to animal prion diseases, occurs worldwide at a case rate of approximately 1 case per 1 million persons.[1] Other variations of human prion disease are reported worldwide at lower rates (see "Disease in Humans" section on the following page). Chronic wasting disease (CWD), a prion disease of wildlife such as deer and elk, is extending its range in the United States and Canada. Scrapie, a prion disease of sheep, continues to affect sheep and goat populations in some parts of the world. The origin, transmissibility, and ability for cross-species infection of these diseases remain poorly understood. Therefore ongoing vigilance for the emergence of TSE-related disease in humans and other animals by human and veterinary clinicians and public health authorities is warranted.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Encourage reporting of human prion disease to public health authorities. CJD is reportable in some states. If it is not reportable in your region, consider adding it to the list of reportable diseases.
- Ensure safety of the blood supply (leukodepletion, screening of donors to exclude those who have resided in high-risk areas).[2]
- Ensure that steps are being taken to reduce the possibility of transmission of prion diseases through organ transplant and infected surgical instruments; see guidelines at http://www.who.int/csr/resources/publications/bse/WHO_CDS_CSR_APH_2000_3/en/.
- In areas where CWD has been reported, educate hunters about measures to reduce the risk of exposure to the CWD agent, including not harvesting deer or elk that appear sick or abnormal; wearing puncture-resistant rubber, vinyl, or latex gloves while dressing carcasses; avoiding contact with brain, spinal cord, and lymphoid tissues; deboning meat; disinfecting knives, saws, and tables with 50% bleach; and having animals tested for CWD.[3]
- Investigate clusters of human cases of neurodegenerative disease.

Human Health Clinicians

- Report suspected cases of iatrogenic CJD, vCJD, or human CWD cases to local and state health departments.
- Conduct an autopsy on suspected human cases and submit tissues for diagnosis to the National Prion Disease Pathology Surveillance Center; see http://www.cjdsurveillance.com/.
- Remove or institute enhanced sterilization procedures on contaminated surgical or dental instruments from practice.[4,5]

Veterinary Clinicians

- Consider the diagnosis of a TSE in cattle, sheep, cats, and other animals with abnormal behavior and progressive neurological deterioration consistent with prion disease.
- Counsel owners and farmers about federal feed restrictions and proper feeding practices to reduce risk of disease transmission.

Agent

TSEs are believed to be caused by abnormal forms (PrP^{sc}) of naturally occurring (PrP^{C}) cellular prion proteins.[6] These misshapen prion proteins are capable of self-replication and transmissibility and form protease-resistant deposits in the brains of infected animals. For many years, TSEs were referred to as *slow virus infections* because of their transmissibility, resistance to filtration, and long latent periods. Most pathologic features of prion diseases involve the CNS. TSE agents, such as the agent of scrapie, are remarkably resistant to disinfection and inactivation by heat, radiation, or chemicals,[7] although more robust disinfection strategies are effective.[8] Strains differ between abnormal prions infecting different species, possibly related to variations in the three-dimensional protein structure or length and sequence of the amino acid chain. The BSE agent has been transmitted experimentally, using a variety of techniques and doses, to other species, including cats, mice, pigs, sheep, goats, cattle, mink, macaque monkeys, and marmosets.[9]

Geographical Occurrence

vCJD has been reported mostly in the United Kingdom, with smaller numbers of cases reported elsewhere in Europe and in Japan. Three cases reported in the United States and one case reported in Canada are believed to be the result of exposure to the BSE agent overseas. In addition to the United Kingdom, BSE has been reported in smaller numbers in most other European countries and in Japan, Israel, Canada, and the United States.

Cases of feline spongiform encephalopathy (FSE) were reported in captive felids in zoos in the United Kingdom and domestic cats in the United Kingdom and Europe. Cases have declined greatly since a ban on bovine spleen and CNS tissue in cat foods.[2]

CWD of deer and elk occurs primarily in an endemic area of Colorado and Wyoming. In recent years, CWD has been detected in neighboring states, as well as in Wisconsin, Illinois, West Virginia, New York, and in the provinces of Alberta and Saskatchewan in Canada.

The prevalence of scrapie among sheep in the United States has been estimated at approximately 0.2%, based on voluntary surveillance.[10] Scrapie is considered eradicated from Australia and New Zealand.

Transmissible mink encephalopathy (TME), first described in 1947, has occurred sporadically in the United States, Canada, Finland, Germany, and Russia.

Groups at Risk

Groups at increased risk for vCJD include those who resided in the United Kingdom during the BSE epidemic and consumed beef products. Hunters are at risk of exposure to CWD in deer and elk through dressing carcasses and meat consumption. Similarly, persons working with sheep and goat carcasses may have some exposure to the scrapie agent, and mink farmers may have exposure to TME. To date, no cases of TSEs related to CWD, FSE, or TME exposure have been described in humans.[11]

Hosts, Reservoir Species, Vectors

BSE is a disease of cattle, but concurrent with the BSE outbreak in the United Kingdom, a similar disease tied to BSE-contaminated feed consumption appeared in other bovids kept in zoos, including kudu, eland, oryx, gemsbok, bison, nyala, and Ankole (exotic ungulate encephalopathy).

FSE has been found in fewer than 100 domestic cats and captive felids, including cheetahs, pumas, ocelots, and a tiger.[9]

CWD occurs in captive and free-ranging Cervidae, including mule deer, white-tailed deer, and elk, and has been detected in a moose.

Scrapie occurs in sheep and goats.

Mode of Transmission and Life Cycle

Transmission of BSE, vCJD, FSE, and TME is believed to be due to ingestion of contaminated animal products (Figure 9-145). Scrapie can be transmitted horizontally in flocks. In addition, maternal transmission appears to play a role in scrapie infection.[12] Person-to-person transmission of vCJD has been reported through contaminated blood products, possibly due to the persistence of the agent in lymphocytes. CWD transmission appears related to both direct contact between animals and indirect contact with contaminated environments.

Environmental Risk Factors

Transmission of iatrogenic CJD involves contaminated articles such as surgical instruments. For other TSEs, the role of environmental contamination is less clear. CWD is spread horizontally between deer and elk, and such transmission is believed to be due in part to environmental contamination, leading to ingestion of the agent.[3] Research is focusing on the role of saliva in the environmental spread of disease. Scrapie may also be transmitted through pastures contaminated with birth products from an infected animal.[3]
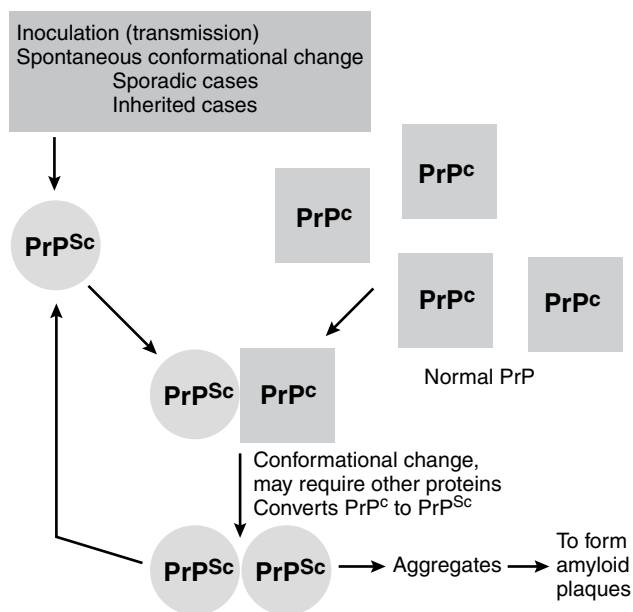
Figure 9-145 ■ Prion protein. In prion diseases (spongiform encephalopathies), PrP *(PrP^c)*, a normal neuronal protein, is converted to an abnormal β-pleated sheet isoform *(PrP^Sc)* through the interaction of PrP^Sc with PrP^c. (From McGavin MD, Zachary JF: *Pathologic basis of veterinary disease*, ed 4, St Louis, 2007, Mosby Elsevier.)

Disease in Humans

At least four different prion-related diseases have been reported in humans, all chronic and invariably fatal neurodegenerative conditions. These include CJD, Gerstmann-Sträussler-Sheinker syndrome (GSS), fatal familial insomnia (FFI), and kuru. Of these, CJD is the most common.[2] GSS and FFI are genetically mediated diseases, whereas kuru transmission has been linked to cannibalism among islanders in the South Pacific.

CJD has three main variants: sporadic CJD (sCJD), iatrogenic CJD, and variant CJD (vCJD). vCJD is associated with BSE. Recently a new type of CJD has been described, known as *proteinase-sensitive prionopathy* (PSPr).[13]

Iatrogenic CJD is a rare form of CJD that has been linked to corneal transplants, growth hormone derived from pituitary extracts, dura matter grafts, and contaminated neurosurgical instruments.[7]

sCJD is characterized by a rapidly progressive dementia with confusion and often associated movement disorders such as ataxia and myoclonus. It is typically a disease of older individuals (median age, 68 years). In sCJD the electroencephalogram (EEG) may show periodic high-voltage complexes. Samples of CSF are acellular with normal glucose but may show elevation of protein including a protein known as 14-3-3.[14]

vCJD differs from sCJD in a number of ways, including the younger age of patients (median age, 28 years), the prominent symptoms of paresthesias, the lack of specific EEG findings, specific MRI findings of an increased signal in the posterior thalamus, and the ready detection of the agent in lymphoid tissue. Patients with vCJD also have a prolonged clinical course compared with patients with sCJD (median illness duration of 13 to 14 months vs. 4 to 5 months for sCJD).[7]

Disease in Animals

BSE initially presents with subtle locomotive and behavioral abnormalities that progress over a period of months. Cattle spend decreased time ruminating and demonstrate increased nose licking, sneezing, nose wrinkling, head tossing, and teeth grinding. An increased startle response can develop, but undisturbed animals may develop paresis, ataxia, and falling episodes. Weight loss and decreased lactation can occur. Recumbency (downer cow), coma, and death occur weeks to months later (Figure 9-146).

An atypical form of BSE has been reported to be due to a variant prion causing a disease termed *bovine amyloidal spongiform encephalopathy* (BASE). The molecular form of this new bovine PrPsc resembles that found in a particular form of human sporadic CJD.[6]

CWD of elk and deer produces subtle changes in behavior and weight loss (Figure 9-147). A spectrum of symptoms including loss of fear of humans, somnolence, and hyperexcitability may occur. Late disease manifests with increased water consumption, increased salivation, low head carriage, a fixed stare, and chronic weight loss despite continued feed intake.[3]

FSE produces an increase in aggressive or shy behavior, ataxia, and increased sensitivity to sound or touch. On biopsy of cases, spongiform degeneration of the neuropil of the brain and spinal cord have been described (Color Plate 9-74).[9] Death occurs within 6 to 8 weeks of onset of signs.

Scrapie also has an insidious onset, with behavioral changes including increased excitability. Tremors of the head and neck (tremblante du mouton) may occur, as can seizures. Intense pruritus develops, leading to loss of fleece over body areas (Figure 9-148).

TME produces abnormal behavior, including increased excitability, tremors, circling, and biting. The disease progresses to death within weeks or months. Table 9-67 compares clinical presentations of TSEs in humans and other animals.

Figure 9-146 ■ Cattle, such as the one pictured here, affected by BSE experience progressive degeneration of the nervous system. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy U.S. Department of Agriculture Animal and Plant Health Inspection Service, Washington, DC.)

Figure 9-147 ■ Clinical chronic wasting disease (CWD) in captive female wapiti (**A**) and free-ranging male mule deer (**B**). The female wapiti had been showing subtle signs of CWD, primarily changes in response to handling and interaction with herd mates, for more than 6 months before the photo was taken. The wapiti was euthanized about 3 months later after signs progressed, although still not to classic end-stage CWD. The male mule deer showed signs that included cachexia, piloerection, diminished alertness, and vacant facial expression (all evident in photo), and mild ataxia also was appreciable when the deer moved. (From Fowler ME: *Zoo and wild animal medicine: current therapy*, ed 6, St Louis, 2008, Saunders Elsevier. *A*, Courtesy M.W. Miller; *B*, courtesy S.W. Miller.)
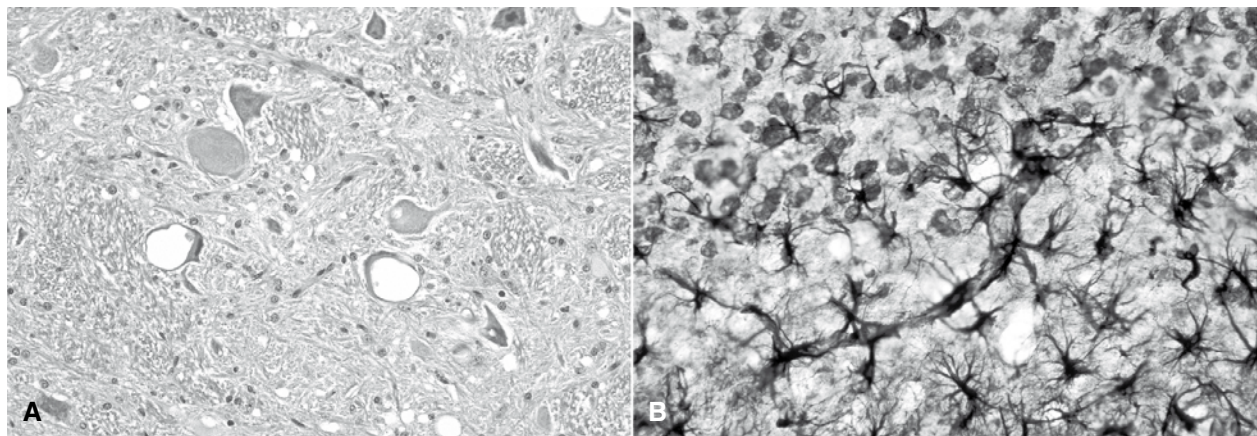

Figure 9-148 ■ Spongiform encephalopathy (scrapie), brain, motor neurons, sheep. **A,** Neuronal cell bodies contain one or more discrete and/or coalescing clear vacuoles. There are no inflammatory cells in this disease. Similar spongiosis is evident in the neuropil (hematoxylin-eosin stain). **B**, Scrapie, experimental, brain, cerebellum, mouse. The cerebellar granule cells are at the top of the figure. There is notable hypertrophy and proliferation (astrocytosis) of astrocytes and their fibers (astrogliosis) (black branching fibers). Some of the processes (running diagonally across the illustration) end, as is normal for astrocytes on the walls of capillaries. Cajal's gold sublimate stain was used for astrocytes. (From McGavin MD, Zachary JF: *Pathologic basis of veterinary disease*, ed 4, St Louis, 2007, Mosby Elsevier. *A*, Courtesy D. Gould, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, and M. McAllister, College of Veterinary Medicine, University of Illinois. *B*, courtesy W.J. Hadlow.)

Diagnosis

The differential diagnosis of CJD in humans includes other causes of dementia, such as Alzheimer's disease, Lewy body dementia, normal-pressure hydrocephalus, neurosyphilis, hypothyroidism, HIV-associated dementia, and senile dementia. The diagnosis of vCJD should be suspected in any person who has resided in a BSE area who presents with behavioral abnormalities and sensory complaints accompanied by signs of dementia. Suspected cases should be referred to a qualified neurologist for definitive diagnosis.[15] MRI findings of ribbons of cortical hyperintensity or basal ganglia or thalamic hyperintensity can help suggest the diagnosis.[17]

The disease can be diagnosed by brain biopsy showing spongiform changes and the presence of the prion protein PRP[sc] (Figure 9-149). Other tests include tonsillar biopsy for PRP[sc] as well as CSF testing for the stress protein 14-3-3, which is elevated in some patients with CJD, although it occurs in other conditions as well.[18]

Table 9-67 ▪ Transmissible Spongiform Encephalopathies: Comparative Clinical Presentations in Humans and Other Animals				
Species/Disease	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**	**Laboratory Findings**
Humans: vCJD	Linked to bovine spongiform encephalopathy	Unknown	Younger age than sCJD; confusion, progressive dementia, paresthesias, ataxia	MRI increased signal in posterior thalamus
				Abnormal EEG
				Elevated CSF 14-3-3 protein
				Tonsil biopsy may show PrPSc[6]
			Illness duration 13-14 months	
Humans: sCJD	Idiopathic	Unknown	Older individuals; confusion, progressive dementia, ataxia, myoclonus	EEG may show periodic high-voltage complexes
			Illness duration approximately 6 months[15]	
Cattle: BSE	Linked to consumption of contaminated feed	Months to years	Abnormal behavior, abnormal movements, staring, exaggerated startle reflex, falling	ELISA or Western blot analysis on brain tissue, with confirmation by immunohistochemistry
Other bovids: exotic ungulate encephalopathy				
Cats: FSE	Linked to consumption of BSE-infected foods	Weeks to months	Abnormal behavior, increased sensitivity to touch	Spongiform degeneration of neuropil on biopsy
Mink: transmissible mink encephalopathy	Thought to result from consumption of foods infected with scrapie or other TSE agent	7-12 months	Increased aggression, biting, circling	Neuropil vacuolation on brain biopsy[9]
Deer, elk: chronic wasting disease	Origin unknown, possibly scrapie	1.5-3 years	Behavior changes, weight loss, staring, low head carriage	Immunochemistry, ELISA, Western blot of brain tissue and/or lymph nodes
Sheep, goats: scrapie	Susceptible genotypes[16]	2-3 years	Excitability, tremors, pruritus with loss of fleece	ELISA or Western blot analysis of brain tissue postmortem or by biopsy of lymphoid tissue

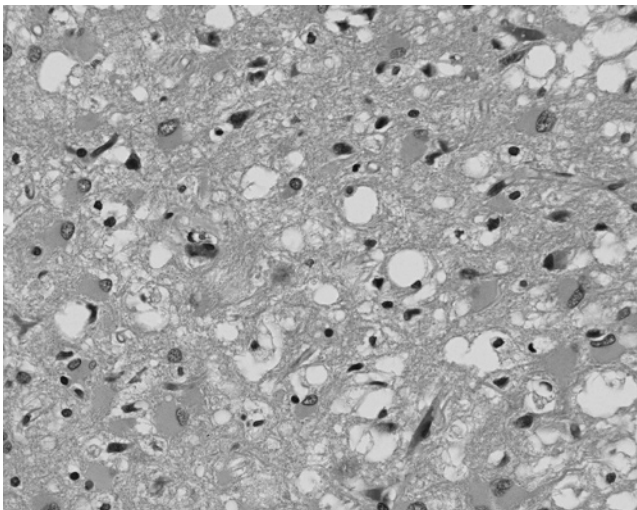*EEG,* Electroencephalogram; *MRI,* magnetic resonance imaging.

Figure 9-149 ▪ Magnified (×100) and stained with hematoxylin-eosin staining technique, this light photomicrograph of brain tissue reveals the presence of prominent spongiotic changes in the cortex and loss of neurons in a case of variant Creutzfeldt-Jakob disease. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Teresa Hammett.)

In cattle, BSE is often diagnosed by ELISA or Western blot analysis on brain tissue with confirmation by immunohistochemistry.

CWD can be diagnosed by immunohistochemistry, Western blot, or ELISA on brain and/or lymph nodes.

Scrapie diagnosis is usually by ELISA or Western blot analysis of brain tissue postmortem, or by biopsy of lymphoid tissue (retropharyngeal, third eyelid, or rectal mucosa).

Treatment

At present, CJD and other prion diseases in humans are fatal neurological diseases without proven effective therapies. There is ongoing research for development of vaccines and for potential compounds with anti-prion activity.[14,19,20,21]). Current treatment of affected humans is limited to alleviating symptoms and patient comfort. Affected animals should be euthanized and removed from the food supply.

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TUBERCULOSIS AND OTHER MYCOBACTERIAL INFECTIONS

Elena Hollender and Peter M. Rabinowitz

Tuberculosis (ICD-10 A15-A19), Non-tuberculous mycobacterial disease (ICD-10 A31)

Other names in humans: TB; atypical mycobacterial infection, MAI, MAC, *Mycobacterium marinum*, leprosy

Other names in animals: TB; mycobacteriosis, avian tuberculosis

Tuberculosis (TB), an infectious, granulomatous disease, is one of the oldest recognized diseases in humans and animals and exemplifies the close parallels between human and animal health. *Mycobacterium tuberculosis* complex (MTBC), which includes *M. tuberculosis* and *M. bovis,* has been found in Egyptian and New World mummies[1,2] and recovered from spinal and bone lesions of Iron Age human remains in Britain and South Siberia.[3,4] In animals, there is documentation of TB in buffalo in China more than 500,000 years ago.[5] TB is believed to have been a key factor in the extinction of mammoths and mastodons around 10,000 years ago.[5]

Approximately one third of the world's human population, or about 2 billion people, are infected with TB; active cases of TB in 2006 were reported to exceed 9 million.[6] Coinfection with HIV disease accounts for more than 15 million cases of TB infection, and TB is an important cause of HIV-related deaths throughout the world. TB has now become the leading cause of death from any infectious disease worldwide, with mortality from tuberculosis in 2006 of 1.7 million.[6]

TB in livestock and wildlife is a worldwide problem and has serious socioeconomic ramifications, especially in developing nations. In the United States, recent surveillance has shown a resurgence of TB in animals among diverse species such as white-tailed deer,[7] bobcats, coyotes, opossums, raccoons, and red foxes.[8,9]

Although the public health linkage between TB in humans and other animals has been recognized for more than a century, the key issue was believed to be human infection with bovine TB through the ingestion of unpasteurized dairy products. However, recent advances in molecular diagnosis have shed light on additional human-animal TB issues including occupational and reverse zoonotic infection. This section discusses TB in humans and other animals. Infection with non-tuberculous mycobacteria (NTM) is covered in an accompanying summary.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

The control of TB in both humans and other animals relies on similar basic practices and principles:

- Identify, test, and treat/manage high-risk populations.
- Physically isolate or separate cases from other people or animals.
- Ensure appropriate medical treatment and management of the case and/or livestock and herd management.
- Provide case investigation.
  - Identify probable routes of transmission, mainly respiratory and gastrointestinal.
  - Identify close contacts of cases to prevent or control secondary cases, including companion animals

and those at high risk of infection; evaluate close contacts for active TB, perform tuberculin skin testing of contacts, treat close contacts if indicated, and work with agriculture officials to cull livestock if indicated.

- o Address issues of ongoing transmission; identify potential human or animal sources of infection, shared common sources (human or animal congregate living facilities, congregate areas of potential exposure, such as waiting rooms, holding pens), and infected food or water supply (unpasteurized dairy products, especially from endemic countries).

- Encourage communication and consultation between human and veterinary public health programs and awareness of the national and local incidence and prevalence of TB in human, domestic animal, and wildlife populations.
- Encourage coordination and consultation between veterinary and human public health programs for contact investigation and recommendations for companion or household animals of active human TB cases and human contacts of veterinary TB.
- In endemic areas, encourage coordination between local agricultural and wildlife agencies regarding testing and control in domestic livestock and wildlife.
- Educate the public regarding possible means of transmission of zoonotic TB, such as consumption of unpasteurized milk and dairy products, especially from, or in, countries with endemic TB.
- Educate hunters of wildlife such as bison, deer, elk and other Cervidae and feral swine in areas of endemic zoonotic TB regarding the infection control precautions, such as gloves and protective clothing to be used when dressing and handling meat and disposing of carcasses.
- Educate medical and veterinary health clinicians regarding TB and zoonotic TB, occupational risks factors such as zookeepers and exotic animal handlers, the possibility of interspecies transmission. See veterinary guidelines at http://www.aphis.usda.gov/animal_health/animal_diseases/tuberculosis/ and at http://www.oie.int/eng/normes/mmanual/2008/pdf/2.04.07_BOVINE_TB.pdf.

Human Health Clinicians

- Immediately report cases to public health authorities: state and local public health TB programs (for a case definition, see http://www.cdc.gov/ncphi/disss/nndss/casedef/tuberculosis_current.htm; a list of state TB control offices can be found at http://www.cdc.gov/tb/pubs/tboffices.htm).
- Ensure that workers in high-risk occupations are using appropriate biosafety procedures.
- If treating a patient with active TB, determine whether pets are in the household and could have been exposed. If so, recommend veterinary evaluation.
- Inquire about occupational risk factors for zoonotic TB and ensure that workers at risk (such as zookeepers) are monitored with baseline and yearly tuberculin skin tests.

Veterinary Clinicians

- Isolate and screen herd replacements.
- Quarantine infected herds, test and slaughter to eradicate infection, and disinfect facilities where infected animals have been housed.
- Report animals with positive test results to agriculture officials and notify public health authorities.
- Ensure proper biosafety procedures are followed in the veterinary facility and that staff are aware of signs of infection in humans and other animals.
- Consider TB in animals living in a household of a human case of TB or with other close contact with a human case (if this human information is presented).
- Pulmonary or disseminated TB in a companion animal should suggest the presence of, or close contact with, active human TB. Communication with local public health officials may alert them to the possibility of an undiagnosed active TB case or provide valuable epidemiological data regarding an already known case. If applicable, contact investigation may be considered for both humans and/or other animals.
- When draining cutaneous lesions or performing a necropsy on an animal with suspected TB, use protective equipment including N-95 respirator, gloves, and eye protection.
- Disinfect surfaces with 1% sodium hypochlorite, 70% ethanol, or iodine solutions.

AGENT

Mycobacteria are nonmotile, rod-shaped, obligate aerobic bacteria classified as acid-fast because of the impermeability of their thick, waxy coats to certain dyes and stains. There are more than 120 species of mycobacteria, which are generally divided into rapidly growing (visible on culture within 7 days) and slow growing (those requiring longer periods of growth). Most mycobacteria are not considered pathogenic. The species of greatest pathogenicity to humans and other animals are those classified as *Mycobacterium tuberculosis* complex (MTBC), the etiologic agents of TB. Of all the mycobacteria, only MTBC and *M. leprae* (the agent of leprosy) are obligate intracellular organisms; the others live freely in the environment.

Because of the importance of MTBC as a pathogen to humans and other animals, other mycobacteria are generally referred to as *nontuberculous mycobacteria* (NTM) or *mycobacteria other than tuberculosis* (MOTT). However, as they are found throughout the environment, they may also be referred to as *environmental mycobacteria* (EM). These NTM are discussed below in a separate section.

Mycobacterium Tuberculosis Complex

MTBC is a highly successful clonal group pathogen of both humans and other animals that includes the species *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. canettii*, *M. caprae*, *M. microti*, and *M. pinnipedii* (Table 9-68). In the past, human TB was thought to be caused solely by *M. tuberculosis*, except for zoonotic cases of *M. bovis* acquired through contact with

Table 9-68 ▪ MTBC and Common Hosts	
Species	**Common Hosts**
M. africanum	Humans and cattle (Africa)
M. bovis	Widest host spectrum; humans, mammalian vertebrates
M. canettii	Humans (immunocompromised)
M. caprae	Goats, cattle, wild boar, pigs, humans
M. microti	Rodents, humans (immunocompromised)
M. pinnipedii	Seals
M. tuberculosis	Humans, vertebrates (e.g., cattle, primates, elephants)

unpasteurized dairy products. Similarly, TB in cattle (bovine TB) was believed to be caused only by *M. bovis.* However, recent breakthroughs in molecular analysis and mapping of the genomic sequence of *M. tuberculosis* have led to a new understanding of the pathogenesis, host range, evolution, and phenotypic differences within the MTBC, including the discovery of interspecies disease by most members of the MTBC, that challenge previous assumptions.

TB was traditionally thought to be a zoonotic disease transferred to humans during the neolithic ages through contact between humans and animals domesticated for livestock. It was therefore believed that *M. tuberculosis* had evolved from *M. bovis.* There is now evidence that all members of the MTBC evolved from a TB progenitor, *M. prototuberculosis*, estimated to be as old as 3 million years (Color Plate 9-75). In addition, researchers have shown that tubercle bacilli are able to exchange parts of their genome with other strains, a process that is crucial to the adaptation of pathogens to different host species.[10,11]

Geographical Occurrence

Mycobacteria of the MTBC group are found worldwide. Zoonotic TB due to foodborne and occupational exposures occurs more commonly in developing countries.

Groups at Risk

Certain occupational groups are at an increased risk of exposure to TB, including health care workers, exposure livestock workers, workers in zoos and animal parks, and animal care workers in primate facilities (see Chapter 12). For example, there has been zoonotic transmission of *M. bovis* from a diseased white rhinoceros to seven zookeepers.[12]

Along with zoo workers, zoo animals appear to be at an increased risk of potential infection. A multispecies epizootic transmission of *M. tuberculosis* occurred in a metropolitan zoo among Asian elephants, Rocky Mountain goats, a black rhinoceros, and humans.[13] There has also been documented transmission in an exotic animal farm among four elephants with *M. tuberculosis* and 11 of 22 handlers, one of whom subsequently had active disease. The isolates for all active cases were identical.[14]

Hosts, Reservoir Species, Vectors

As Table 9-68 shows, different members of the MTBC group are adapted to different host species, although interspecies transmission can occur. TB in wildlife has become a major problem in many parts of the world, and transmission of disease is increasingly bidirectional at the livestock-wildlife interface in industrialized and developing countries. Wildlife reservoirs such as badgers, opossums, ferrets, deer and other cervids, feral pigs, African buffalo, and bison serve as sylvatic reservoirs and ongoing sources of infection to pastured animals primarily through contamination of water and food sources within their shared environment. The presence of multiple maintenance hosts favors the long-term persistence of infection and disease among differing populations.[15,16]

Conversely, infection in wildlife species such as kudu, baboons, lions, and hyenas may represent a sporadic spillover from a livestock reservoir. Therefore TB in livestock and pastured animals will no longer be able to be eradicated or controlled by traditional livestock control programs that do not take into account the wildlife disease reservoirs. In addition to the risks of transmission between wildlife and livestock, wildlife TB can pose a zoonotic threat to game hunters who butcher carcasses (respiratory and cutaneous exposure) and who consume undercooked meat.[17,18] In addition, TB in peridomestic wildlife such as nonhuman primate populations in Asia may pose a risk of direct zoonotic transmission to humans via close contact.

Mode of Transmission and Life Cycle

Infection with TB begins when the organism is introduced into the body, usually by inhaled droplet nuclei containing tubercle bacilli, which when <5 microns reach the pulmonary alveoli (Figure 9-151). The bacilli are then phagocytized by the pulmonary alveolar macrophages and destroyed or contained. The alveolar macrophages are an important part in the initiation of the host's immune response to the mycobacteria. Antigen of the tubercle bacilli then stimulates the host's cellular immune response and the immune cascade is triggered. Immunologic control or containment of the infection is achieved through a potent cell-mediated immune response beginning with helper T-lymphocytes and, later, a delayed hypersensitivity response. This immune response also involves the production of proinflammatory cytokines, especially interferon-gamma (IFN-γ), tumor necrosis factor (TNF), and interleukin-1.

The spread of the infection may be halted by the immune system at the local lymph node level. However, because cellular immune response usually takes between 4 and 12 weeks to be elicited, it may not, or only partially, be stopped there. The MTBC bacillus may then spread systemically via the regional lymph nodes and lymphatic system and enter the bloodstream (primary disease). Hematogenous circulation of the tubercle bacilli is generalized but may affect mainly organs and tissues that are more densely vascularized, such as bone, liver, spleen, central nervous system, kidneys, and genital tract, where the bacilli are then targeted by local mononuclear phagocytes. These organs, along with lymph nodes, are therefore the most common sites of extrapulmonary disease. Studies of tissue from infected asymptomatic individuals have shown viable

M. tuberculosis in primary lesions in the lung and in lesion-free areas of lung and lymph nodes. Although primary lesions can occur anywhere in the lung, postprimary disease most commonly develops in the apical regions.[19] The immune system continues to attempt to isolate the bacillus, forming granulomas or *tubercles* (Color Plate 9-76) The granuloma may become thick walled and dense, effectively encapsulating the organism and preventing further spread. The bacilli then become latent within the granulomas. These granulomas may eventually calcify.

The major route of transmission for humans (and one of the main routes for animals) is through respiratory aerosolization. When there is active TB in the lungs, the bacillus is expelled and aerosolized in the form of droplet nuclei through coughing (or any explosive respiratory action such as singing, shouting, sneezing, or talking). For these droplet nuclei to be inhaled and reach the alveoli in humans, they must be 3 to 5 microns or less in size. In animals, the exact sizes of infecting droplet nuclei may vary depending on the species.

Other risk of exposure to infectious aerosols includes opening an infected chest cavity such as during autopsy, necropsy, or slaughter of livestock, as well as hosing down an area where an infected animal has been housed. The efficiency of transmission of TB depends on a number of factors, as shown in Box 9-7.[20]

The second most common route of transmission is through the gastrointestinal tract by the ingestion of infected material. Drinking or eating unpasteurized milk products traditionally has been the principal means by which humans have acquired zoonotic TB.[21] In industrialized countries pasteurization and strict herd testing and management have made such gastrointestinal transmission rare, but zoonotic TB caused by *M. bovis* acquired through ingestion may be seen in immigrants from countries with a continuing prevalence of *M. bovis* infection in cattle or livestock.[22,23]

Of note are the recent documented human-to-human transmissions of *M. bovis,* including an epidemiologically linked cluster of six cases identified in the United Kingdom. Five of the patients had pulmonary TB disease and one had TB meningitis[24]; only one was known to be HIV infected. The index case had a history of occupational exposure and consumption of unpasteurized milk and cheese both as a young adult and recently in a country not free from bovine TB. In another cluster, human nosocomial transmission of *M. bovis* among HIV-infected individuals occurred in a Spanish hospital, resulting in 30 deaths.[25] Humans may also serve as a source of TB infection for animals, including nonhuman primates, cattle, dogs, and macaws.[26-31]

Animal-to-animal transmission of TB occurs through respiratory and gastrointestinal routes.[32] Respiratory infection can occur in herds or closely quartered animals through pulmonary disease or draining lymphadenopathy. Infection is also acquired by ingestion of infected meat, sharing of infected water and food sources, grooming, and exposure to secretions.

Environmental Risk Factors

Because a major influence on the aerosol transmission of TB in humans and other animals is the closeness and duration of contact with the infected individual, population density can be a key environmental factor driving TB transmission. Although being outdoors significantly decreases the risk of transmission, the close or sheltered outdoor housing of animals and humans may decrease that advantage. Contaminated water can be another environmental risk for disease transmission in animals.

Disease in Humans

During primary and latent infection, the person does not exhibit signs of disease and is not considered infectious. Immunocompetent individuals will develop a balance between host and mycobacteria, and the infection will remain latent. However, if there is a breakdown of the host's immune function and the infection is no longer able to be effectively contained, active disease may develop (Figure 9-150).

More than 90% of humans infected with MTBC maintain control of the infection through immune mechanisms during their lifetime. These individuals have an approximately 10% chance of developing active TB disease during their lifetime: 5% within the first few years of infection (progressive primary TB disease) and 5% at a later stage in their lives (reactivation TB disease). However, that probability of progressing to active disease is significantly increased in the presence of comorbid conditions that compromise immune function. Factors associated with this increased risk are outlined in Box 9-8.

HIV exerts a significant adverse affect on the pathogenesis of TB. With a suppressed or poorly functioning immune system, the host will release an immature response to the tubercle bacillus. The decrease in the number and function of T-cell lymphocytes as a result of HIV disease weakens the immune reaction and the host cannot, or only poorly, contain the TB organisms that are present. There is a greater chance of rapid progression from infection to disease after recent TB infection. There is also a question of whether an individual with HIV has an increased chance of infection with TB from the loss of innate resistance. People with HIV have an 8% to

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BOX 9-7   *FACTORS DETERMINING TRANSMISSION OF TUBERCULOSIS*

Characteristics of the Source Case
- Concentration of organisms in sputum
- Presence of cavitary disease
- Frequency and strength of cough

Characteristics of the Exposed Individual
- Previous tuberculosis infection
- Innate resistance to tuberculosis infection
- Genetic susceptibility to tuberculosis infection/disease

Characteristics of the Exposure
- Frequency and duration of exposure
- Dilution effect (volume of air containing infectious droplet nuclei)
- Ventilation (turnover of air in a space)
- Exposure to ultraviolet light, including sunlight

Virulence of the Infecting Strain of *Mycobacterium Tuberculosis* Complex

Adapted from CDC "Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf.
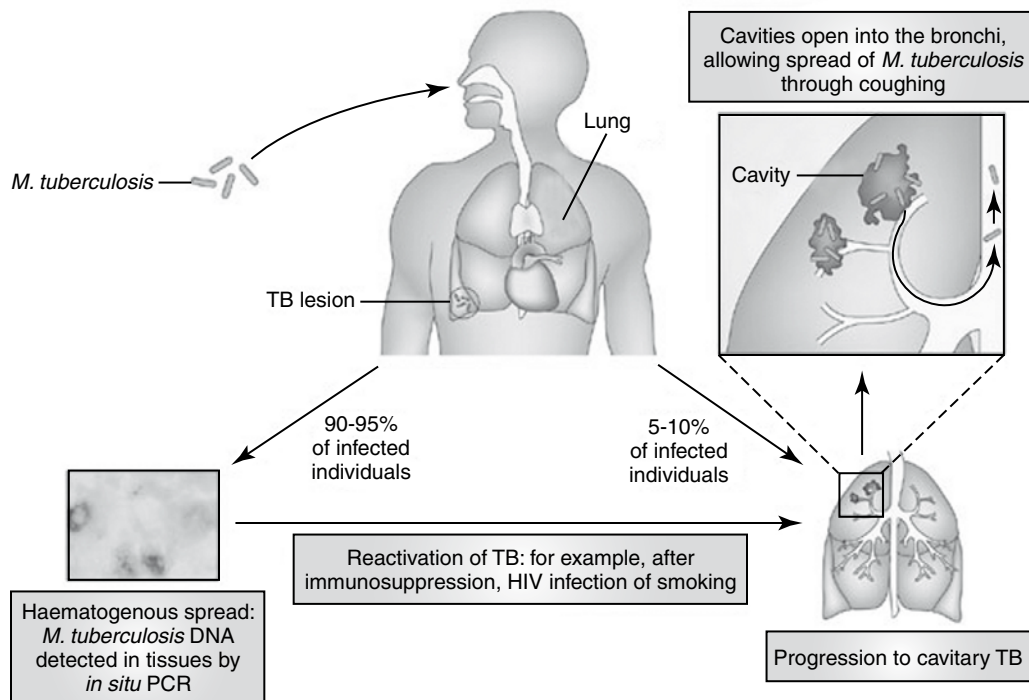
Figure 9-150 ■ Phases of infection with tuberculosis. (From Rook GA, Dheda K, Zumla A: Immune responses to tuberculosis in developing countries: implications for new vaccines, *Nat Rev Immunol* 5(8):661-7, 2005.)

BOX 9-8   *RISK FACTORS FOR DEVELOPING TUBERCULOSIS DISEASE*

- Recent TB infection (within past 2 years)
- HIV infection
- Chest radiographic findings suggestive of previous TB
- Contact with a recent case of active TB
- Recent immigration from tuberculosis-endemic country within 5 years of immigration
- Malnutrition
- 10% below ideal body weight
- Alcohol and drug abuse (especially IV drugs)
- Newborn, infants <2 years
- Comorbid medical conditions:
  - Diabetes
  - Gastrectomy or jejunoileal bypass (total or partial)
  - Silicosis (affects pulmonary macrophage function)
  - Cancer (especially head and neck tumors)
  - Hematologic malignancies (leukemia, lymphoma)
  - Chronic renal failure
  - Solid organ transplant (chronic immunosuppressive therapy)
- Immunosuppressive conditions, including:
  - Cancer chemotherapy
  - Prolonged treatment with corticosteroids
  - Treatment with anti-TNFα agents

10% chance per year to progress from infection to active TB. The 1-year mortality rate for treated, HIV related TB is 4 times the rate of non-HIV related TB, around 35%. TB also worsens HIV disease by inducing stimulation and replication of T-cell lymphocytes. These T cells are then targeted by the virus, resulting in increased HIV replication. If the tuberculous infection is initially contained by the immune system, which then subsequently experiences a significant deterioration in the quantity and function of T-helper cells, the bacillus may no longer be contained and the TB reactivates. In addition, the cytokines produced in response to TB infection stimulate the production of HIV in vitro.[33]

Active TB is usually a slowly progressive disease characterized by systemic symptoms of weight loss, fatigue, anorexia, fevers, chills, night sweats, and wasting. The severe weight loss and wasting associated with the disease led to its former name of *consumption.* When the disease is pulmonary, presenting symptoms may also include a persistent cough (with or without sputum production), chest pain, and hemoptysis. Although TB is generally a chronic, debilitating disease, it may present with an acute, rapidly progressing course. Disease is generally pulmonary, followed by lymphatic drainage and local lymphadenopathy, or disseminated (especially in immunocompromised hosts; Color Plate 9-77). Manifestations may vary depending on the extrapulmonary site of disseminated disease. Central nervous system involvement may present as either meningeal or parenchymal disease. Meningitis more commonly affects the basilar meninges, and the cranial nerves may also be involved. Parenchymal lesions may be single or multiple and present as solid tuberculomas or TB abscesses. Symptoms will depend on the location of the lesion and/or mass effect from surrounding edema (Figure 9-151). TB may also present in the spinal vertebrae (Pott's disease) (Figure 9-152).

Figure 9-151 ▪ A magnetic resonance image of tuberculoma in a child with culture-positive tuberculous meningitis. The child's presenting signs and symptoms included fever, altered mental status, and hemiparesis. (From Gershon AA, Hotez PJ, Katz S: *Krugman's infectious diseases of children*, ed 11, St Louis, 2004, Mosby Elsevier.)

Disease in Animals

As in humans, TB can be either a chronic or rapidly progressive disease, with the clinical signs varying greatly according to the species involved. As with humans, it is believed that many animals infected with MTBC remain in a latent phase, although the natural history is less well understood.

In cattle, TB is often not apparent, and therefore not diagnosed, until terminal stages of the disease; it is often found only at necropsy or in abattoirs (Color Plate 9-78). This, unfortunately, allows for a prolonged period of transmission. The initial presentation, besides cachexia, progressive weakness, and anorexia, may also include cough, lymphadenitis, and draining sinus tracts, especially around the neck, face, and chest. In later stages, lymph nodes may be enlarged to the point of impingement on airways, gastrointestinal (GI) tract, or blood vessels.[34] GI tract involvement may be manifested by diarrhea or constipation. The female genital tract may be involved. At necropsy, both tuberculous granulomas and abscesses may be present.

In Cervidae, which include deer, antelope, moose, elk, and reindeer, TB has been found in both farmed and free-living animals. The course may be chronic and progressive or acute. The presentation is similar to that found in cattle with granulomas, but thin-walled abscesses are also common.

In nonhuman primates, as in humans, there is a broad clinical spectrum of disease, including latent TB, chronic

Figure 9-152 ▪ **A,** Vertebral tuberculosis. **B,** Tuberculosis of the spine (Pott's disease). **C,** Kyphosis is secondary to anterior destruction of vertebral bodies resulting in wedging of adjacent vertebrae and loss of disk space clearly seen by radiography. (From Cohen J, Powderly WG: *Infectious diseases*, ed 2, Philadelphia, 2004, Mosby Elsevier. *A* and *B,* Courtesy J. Cohen, Brighton, U.K. *C,* Courtesy A. Wightman.)

primary TB, rapidly progressing and fulminant disease, and reactivation TB.[35] Old World species appear to be more susceptible than New World species.

Culture-confirmed cases of TB have been diagnosed in at least 36 elephants in the United States from 1994 to 2006.[36] It has been reported in captive elephants, primarily Asian, although the potential for transmission to wild elephants is increasing. Clinical disease in elephants usually has a chronic, debilitating presentation. Signs may not be present until the disease is advanced and include weakness, weight loss, and coughing, although they may also be specific to the organ system involved, such as chronic vaginal discharge or conjunctivitis.

TB also occurs in domestic and companion animals. Dogs and cats may present with a typical clinical picture of wasting, anorexia, and progressive decline. If the MTBC was acquired through the respiratory tract, signs may also include cough and shortness of breath; if acquired through the ingestion of infected meat or milk, GI signs may be present.

Diagnosis

Active Disease

The key factor in the diagnosis of active TB is that of clinical suspicion based on the presenting history, signs or symptoms, chest radiograph, and/or laboratory testing. Microscopy looks for the presence of acid-fast bacilli (AFB) on direct smears of clinical specimens. The finding of AFB indicates the presence of mycobacteria but not the specific species.

Identification of the mycobacterial species is through culture or molecular testing such as polymerase chain reaction. A tissue biopsy specimen may show characteristic histological findings, such as granuloma, caseation, necrosis, calcification, and typical cellular immune response. The presumptive diagnosis of TB (mycobacteriosis) may be made on this basis, especially in animals.

Cultures may use liquid media, such as the mycobacteria growth indicator tube (MGIT, BBL Becton Dickinson Microbiology Systems, Cockeysville, Md.) and/or solid agar media, such as Bactec (Becton-Dickinson Diagnostic Instrument Systems, Sparks, Md.) Lowenstein-Jensen, or Middlebrook 7H10. MTBC is a slow-growing organism that replicates approximately every 24 hours. Growth in liquid media usually occurs within 1 to 3 weeks, whereas growth on solid media may be 6 to 8 weeks. Drug susceptibility testing is performed on isolates of MTBC routinely for isoniazid, rifampin, pyrazinamide, and ethambutol.

Since the genetic mapping of MTBC, molecular testing has been used in the diagnosis of TB. Nucleic acid amplification (NAA) tests, such as the *Mycobacterium tuberculosis* Direct (MTD) test (Gen-Probe, Inc., San Diego, Calif.) are performed on direct specimen smears based on the presence of MTBC RNA. The sensitivity and specificity of the NAA test on a positive AFB smear are greater than 95% and 99.6%, respectively. PCR is a species-specific DNA-based test used to identify MTBC. Further genotyping on positive TB cultures often may be done, usually by one of two methods:

mycobacterial interspersed repetitive units (MIRU) or spoligotyping. Genotyping is used to assist TB control programs in identifying outbreaks and recent transmission in a more real-time manner so that appropriate secondary testing and management can be performed sooner. Molecular testing of the TB isolate for genetic resistance mutations is beginning to be used.

Thoracic radiographs may be part, or the initial finding, of the clinical presentation of TB in humans and other animals (Figures 9-153 and 9-154). Classically, TB is an upper lobe disease, either unilateral or bilateral. Abnormalities typically are seen in the apical and posterior segments of the upper lobe or the superior segments of the lower lobe; however, lesions may appear in any part of the lungs. Radiographic abnormalities may present as infiltrates, nodules, cavitary lesions, pleural thickening, or a diffuse miliary pattern. Hilar and mediastinal lymphadenopathy may be present, with or without accompanying infiltrates or cavities. Immunosuppressed individuals may present with only hilar or mediastinal adenopathy, or the chest radiograph may appear normal.
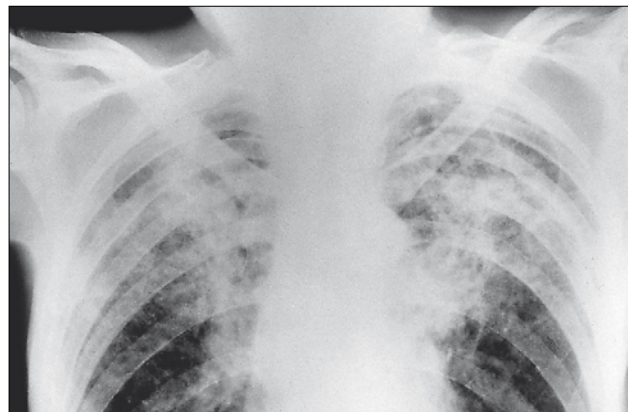

Figure 9-153 ■ Chest radiograph of a patient with pulmonary tuberculosis. There is extensive parenchymal streaking, predominantly in the upper fields of the lungs. These changes are typical of chronic bilateral pulmonary tuberculosis. Some enlargement of the heart is also evident. (From Male D, Brostoff J, Roth D et al: *Immunology*, ed 7, Philadelphia, 2006, Mosby Elsevier.)
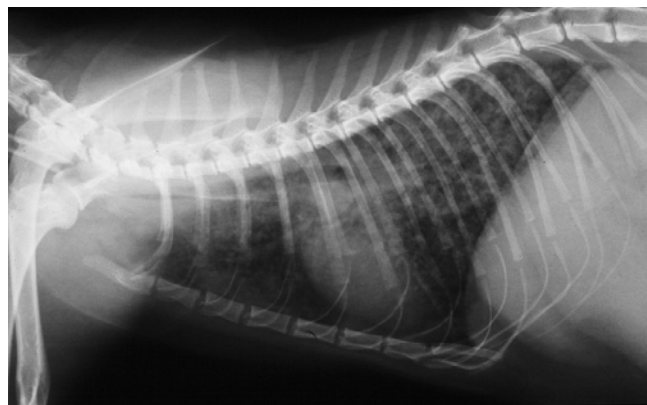

Figure 9-154 ■ Lateral thoracic radiograph of a cat with disseminated *M. bovis* infection. (From Greene CE: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders Elsevier. Courtesy D. Gunn-Moore, University of Edinburgh, Scotland.)

Latent Infection

The tuberculin skin test (TST) has been the standard screening tool for TB infection in humans and other animals (Figure 9-155). It produces a delayed-type hypersensitivity reaction in those with tuberculous infection. It is useful for determining how many individuals in a group are

Figure 9-155 ■ This technician is in the process of correctly placing a tuberculin skin test in this recipient's forearm, which will cause a 6-mm to 10-mm wheal (i.e., a raised area of skin surface) to form at the injection site. The tuberculin skin test is used to evaluate people for latent tuberculosis infection. In the United States, this skin test consists of an intradermal injection of exactly one tenth of a milliliter of tuberculin, which contains 5 tuberculin units. Correct placement of this intradermal injection involves inserting the needle bevel slowly at a 5- to 15-degree angle. The needle bevel is advanced through the epidermis, the superficial layer of skin, approximately 3 mm so that the entire bevel is covered and lies just under the skin surface. A tense, pale wheal that is 6 mm to 10 mm in diameter appears over the needle bevel. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga. Courtesy Gabrielle Benenson.)

infected (e.g., contact investigation) and in the evaluation of those with signs or symptoms or those who are suspected of having TB.

The TST is administered by subcutaneously injecting a preparation of (inactive) mycobacterial antigens. In humans, 0.1 mL of purified protein derivative (PPD) is placed on the inner surface of the forearm. More complete information on TB skin test placement, reading, and interpretation is available at http://www.cdc.gov/TB/pubs/slidesets/core/html/trans4_slides.htm. The TST is usually read after 48 to 72 hours. The induration (not the erythema) is measured and should be recorded in millimeters, not simply as negative or positive. In humans, a positive TST reaction may be measured for up to 7 days, although a negative reaction can only be read until 72 hours. The TST, however, has limited sensitivity and specificity. In humans, there is an overall false-positive rate of 20% and a false-negative rate of 20%. False-positive results may be seen in NTM infection, recent Bacillus Calmette-Guérin (BCG) vaccination, or incorrect administration. False-negative results may occur in overwhelming TB disease, anergy, recent TB infection, newborns, recent live-virus vaccinations, some viral illnesses, incorrect administration, or waning immune response (usually due to age or prolonged time since infection). Because of the possibility of a waning immune response, in some instances a two-step TST is performed. In those situations, an initial TST may serve to stimulate, or boost, subsequent TSTs. A two-step TST is therefore currently recommended for baseline testing in those who will undergo periodic testing, such as health care workers.[37] This helps to differentiate between a boosted reaction and one due to recent infection. The criteria for determining whether a human TST is positive depends on the risk group of the individual. Table 9-69 defines the size of the induration per risk group.

Table 9-69 ■ Criteria for Tuberculin Positivity, by Risk Group

Reaction ≥5 mm of Induration	Reaction ≥10 mm of Induration	Reaction ≥15 mm of Induration
HIV positive status Recent contacts of TB case patients Fibrotic changes on chest radiograph consistent with prior TB Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/day of prednisone for ≥1 month)*	Recent immigrants (i.e., within the past 5 years) from high-prevalence countries Injection drug users Residents and employees† of the following high-risk congregate settings: prisons and jails, nursing homes, and other long-term facilities for the elderly; hospitals and other health care facilities; residential facilities for patients with acquired AIDS; and homeless shelters Mycobacteriology laboratory personnel Persons with the following clinical conditions that place them at high risk: diabetes mellitus, chronic renal failure, some hematological disorders (e.g., leukemias and lymphomas), and other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass Children younger than 4 years or infants, children, and adolescents exposed to adults at high risk	Persons with no risk factors for TB

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.
†For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.
From American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC): Targeted tuberculin testing and treatment of latent tuberculosis infection, *MMWR Morb Mortal Wkly Rep* 49(RR-6):1–51, 2000.

Recently IFN-γ–releasing assays (IGRAs) are being used to detect latent TB infection. Generally these are whole blood assays that measure and compare the amount of IFN-γ released by white blood cells in response to antigens of MTBC. In humans, QuantiFERON-Gold (Cellestic, Inc., Valencia, Calif.) and T-SPOT.TB (Oxford Immunotec, Oxford, U.K.) are examples of assays used.[38]

In other animals, the TST is the only skin test for use in cattle prescribed by the World Organisation for Animal Health.[39] However, there is no standardization of TST testing in animals, as individual protocols are established by each country. In cattle, testing may use *M. bovis* antigen alone (caudal fold test [CFT], cervical test [CT]) or along with *M. avium* (comparative cervical test [CCT]).[8] Test results are read at 72 hours ± 6 hours. The preferred TST placement sites in animals differs by species and include the caudal fold in bovids, ear in pigs, and eyelid in primates.

Skin testing in animals produces high rates of false-positive and false-negative results. These are often from the same interference: mycobacterial species, such as *M. avium* or *M. avium* subsp. *paratuberculosis*, overwhelming or advanced disease, in the face of comorbidity that prevents an appropriate immune response, early infection, or improper test administration.

In cattle, buffalo, bison, and other bovids, several serological tests based on *M. bovis* have been developed and are in use, such as SeraLyte-Mbv (PriTest, Redmond, Wash.) and Chembio Bovid TB STAT-PAK (Chembio Diagnostic Systems, Inc., Medford, NY).[36] There are also assays for use in cervids, primates, badgers, camelids, elephants, and other exotic wildlife, among others.[40]

Treatment

Primary prevention remains the optimum course of disease control. It has proven extremely difficult, if not impossible, to eradicate any public health disease such as TB without an effective vaccine. Currently numerous studies are assessing vaccines for human and differing veterinary populations to prevent infection.

Treatment in Humans

Treatment of active TB uses a combination of antibiotics for a prolonged period of time. The exact regimen is based on or modified according to the organism's susceptibilities. For drug-susceptible isolates, treatment usually is with three or four drugs (isoniazid [INH], rifampin [RIF], pyrazinamide [PZA] with or without ethambutol [EMB]) for the first 2 months, then INH and RIF to complete 6 months' total treatment. Table 9-70 shows drug treatment regimens for pan-susceptible TB.[42] Multidrug-resistant tuberculosis (MDR-TB) is resistant to at least INH and RIF, the two best first-line TB medications. Extensively drug-resistant tuberculosis (XDR-TB) in addition to INH and RIF is also resistant to the best second-line drugs, the fluoroquinolones and an injectable such as kanamycin or capreomycin. The treatment of TB with drug-resistant organisms is more complicated and difficult and should be done by or in consultation with experts. Regimens for resistant TB

Table 9-70 ▪ Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Initial Phase			Continuation Phase		Range of Total Doses *(minimal duration)*	Rating* (Evidence)†	
Regimen	Drugs	Interval and Doses‡ *(minimal duration)*	Regimen	Drugs	Interval and Doses‡,§ *(minimal duration)*		HIVneg	HIVpos
1	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk) *or* 5 days/wk for 40 doses (8 wk)¶	1a	INH/RIF	7 days/wk for 126 doses (18 wk) *or* 5 days/wk for 90 doses (18 wk)¶	182-130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92-76 (25 wk)	A (I)	A (II)¶
			1c#	INH/RPT	Once weekly for 18 doses (18 wk)	74-58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	7 days/wk for 14 doses (2 wk), *then* twice weekly for 12 doses (6 wk) *or* 5 days/wk for 10 doses (2 wk),¶ *then* twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62-58 (26 wk)	A (II)	B (II)**
			2b#	INH/RPT	Once weekly for 18 doses (18 wk)	44-40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)

Table 9-70 ▪ Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms—(*Continued*)								
Initial Phase			**Continuation Phase**			**Range of Total Doses** *(minimal duration)*	**Rating* (Evidence)†**	
Regimen	**Drugs**	**Interval and Doses‡** *(minimal duration)*	**Regimen**	**Drugs**	**Interval and Doses‡,§** *(minimal duration)*		**HIVneg**	**HIVpos**
4	INH RIF EMB	7 days/wk for 56 doses (8 wk) *or* 5 days/wk for 40 doses (8 wk)¶	4a	INH/RIF	Seven days/wk for 217 doses (31 wk) *or* 5 days/wk for 155 doses (31 wk)¶	273-195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118-102 (39 wk)	C (I)	C (II)

From Blumberg HM, Burman WJ, Chaisson RE et al: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis, *Am J Respir Crit Care Med* 167(4):603–62, 2003.
EMB, Ethambutol; *INH,*isoniazid; *PZA,* pyrazinamide; *RIF,* rifampin; *RPT,* rifapentine.
*Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.
†Definitions of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.
‡When directly observed therapy (DOT) is used, drugs may be given 5 days/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice.
§Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.
¶Five-day-a-week administration is always given by DOT. Rating for 5 day/wk regimens is AIII.
¶Not recommended for patients with HIV infection with CD4+ cell counts <100 cells/mL.
#Options 1c and 2b should be used only in HIV negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest radiograph. For patients who start this regimen and are found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

generally use a combination of first- and/or second-line drugs for an extended period of time—between 9 and 24 months depending on the resistance pattern.

Treatment of latent TB infection (LTBI) in humans, previously referred to as *prophylaxis,* is based on the TST risk groups previously discussed. Because current skin test recommendations target high-risk groups, the intent to test is generally the intent to treat. The first-line medication for the treatment of LTBI remains INH, currently recommended for 9 months. An alternative treatment is INH for 6 months. INH regimens may be daily or intermittent. Table 9-71 shows recommended regimens for the treatment of LTBI.

Treatment in Animals

Until recently, the approach to treatment of TB in animals has not included the use of medications to treat until cure, and it is still the rare exception. The overwhelming majority of animals with suspected or confirmed TB are culled or euthanized, such as with cattle. This has been done for several reasons: an effort to halt the spread of the disease to other animals or herds and mitigate the economic loss of herd and trade; the lack of practical alternatives; the difficulty of testing methods to distinguish MTBC disease from infection or from nontuberculous mycobacterial disease; the cost of TB medication regimens; problems with drug administration and monitoring; and the inability or unreliability of monitoring response to disease or LTBI treatment. In non-herd situations or where the animal is of significant economic or species value, such as zoo animals and rare or endangered species, pharmacotherapy has been used. Treatment of elephants with multidrug regimens has been documented, including for MDR-TB.

Due to a paucity of data, the medication dosing for TB in animals has been based loosely on data from human pharmacokinetic studies and dosages. However, the increased use of pharmacotherapy for veterinary TB may result in more species-specific recommendations. For example, a number of pharmacokinetic studies have been done on TB drug levels in elephants.[41-45] Expert consultation is suggested in the treatment of veterinary TB.

The first-line TB medications used in animals are the same as humans: INH, RIF, EMB, and PZA (which is not used in the treatment of *M. bovis* as this organism is usually resistant). Other antituberculous medications also include quinolones and systemic aminoglycosides. Veterinary quinolones used for TB include enrofloxacin and marbofloxacin, and aminoglycosides include amikacin and streptomycin. Nevertheless, much more investigation is needed in the area of veterinary antituberculous pharmacotherapy.

Companion animals rarely are treated for TB, either because of the advanced condition of the animal, belief that TB cannot be treated, or concerns regarding public health. It is probable that many, if not most, cases of TB in these animals have gone undiagnosed as a result of a combination of lack of awareness of the disease, lack of information regarding diagnostics and testing, and the impression that, regardless, treatment is not feasible. That TB in companion animals is an issue of public health concern has been cited as another reason for not considering pharmacotherapy. However, it may be possible in these situations to consider some of the same principles of TB disease control as used in other human and veterinary settings, such as housing the animal separately and/or outdoors while awaiting test results or a response to therapy. Nonetheless, the logistics and feasibility

Table 9-71 ▪ Recommended Drug Regimens for the Treatment of LTBI in Adults

Drug	Interval and Duration	Comments*	Rating† HIV Negative	(Evidence)‡ HIV Infected
Isoniazid	Daily for 9 months§‖	In persons with HIV infection, isoniazid may be administered concurrently with NRTIs, protease inhibitors, or NNRTIs.	A (II)	A (II)
	Twice weekly for 9 months§‖	DOT must be used with twice-weekly dosing.	B (II)	B (II)
Isoniazid	Daily for 6 months‖	Not indicated for persons with HIV infection, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
	Twice weekly for 6 months‖	DOT must be used with twice-weekly dosing.	B (II)	C (I)
Rifampin¶	Daily for 4 months	Used for persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB.	B (II)	B (III)
		In persons with HIV infection, most protease inhibitors or delavirdine should not be administered concurrently with rifampin. Rifabutin with appropriate dose adjustments can be used with protease inhibitors (saquinavir should be augmented with ritonavir) and NNRTIs (except delavirdine). Clinicians should consult Internet updates for the latest specific recommendations.		
RZ	Daily for 2 months	RZ generally should not be offered for treatment of latent tuberculosis infection for persons with or without HIV infection.	D (II)	D (II)
	Twice weekly for 2-3 months		D (III)	D (III)

Adapted from CDC: Targeted tuberculin testing and treatment of latent tuberculosis infection, *MMWR Morb Mortal Wkly Rep* 49(RR-6):1-51, 2000.

*Interactions with human immunodeficiency virus (HIV)-related drugs are updated frequently and are available at http://www.aidsinfo.nih.gov/guidelines.

†Strength of recommendation: A = Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered. B = Moderate evidence for efficacy or strong evidence for efficacy but only limited clinical benefit supports recommendation for use. Should generally be offered. C = Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional. D = Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered. E = Good evidence for lack of efficacy or for adverse outcome support a recommendation against use. Should never be offered.

‡Quality of evidence supporting the recommendation: I = Evidence from at least one properly randomized controlled trial. II = Evidence from at least one well-designed clinical trial without randomization from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results from uncontrolled experiments. III. = Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

§Recommended regimen for persons aged <18 years.

‖Recommended regimens for pregnant women.

¶The substitution of rifapentine for rifampin is not recommended because rifapentine's safety and effectiveness have not been established for patients with latent tuberculosis infection.

NRTIs, Nucleoside reverse-transcriptase inhibitors; *NNRTIs,* non–nucleoside reverse-transcriptase inhibitors; *DOT,* directly observed therapy; *RZ,* rifampin plus pyrazinamide.

of this approach depend on each individual situation, and discussion with TB experts is advisable.

Nontuberculous Mycobacteria

NTM are environmental opportunistic pathogens that differ from the members of MTBC (and *M. leprae*) in that they are not obligate pathogens but rather are found in the environment and environmental reservoirs that serve as the source of infection.[46] Although most NTM do not cause human or animal disease, some may be pathogenic with potential for interspecies and zoonotic transmission. Table 9-72 shows common potentially pathogenic mycobacteria, classified according to growth rate as either rapid growing (less than 1 week) or slow growing (more than 1 week).

Transmission of NTM is achieved through inhalation or ingestion of water, particulate matter or aerosols, or through trauma.[47] NTMs are not generally considered communicable between humans and animals or as zoonotic infections and as such are not reportable diseases. Consequently, epidemiological data on the prevalence of NTM disease are not well established

and surveillance information is limited. The clinical and epidemiological presentation of NTM infection has changed dramatically in recent years. This is thought to be due, in part, to the ability of these organisms to survive and flourish in habitats shared with humans and other animals, such as drinking water. In addition, an increase in the proportion of HIV-infected and other immunosuppressed hosts suggest a continuing and increasing prevalence of NTM infections in the future. Human risk factors associated with NTM disease include comorbid lung conditions such as prior TB disease, silicosis, and bronchiectasis, and host immunosuppression such as HIV infection. With the rise of HIV infection in the 1980s came increasing reports of disseminated human NTM infections, such as *M. avium* complex (MAC).

The most common sites of NTM disease in humans are pulmonary, lymphatic, skin, and soft tissue and disseminated disease. Pulmonary disease, commonly from *M. avium*, *M. intracellulare*, *M. kansasii,* or *M. abscessus*, generally presents as a chronic condition with a persistent or varying cough; additionally, there may be fatigue, malaise, sputum production, fever, weight loss, dyspnea, and hemoptysis.

Table 9-72 ▪ Potentially Pathogenic Nontuberculous Mycobacteria		
Mycobacterial Species	**Growth Classification***	**Disease Presentation**
M. abscessus	Rapid	Pulmonary, skin, soft tissue, bone
M. avium complex: *M. avium*, *M. intracellulare*, *M. paratuberculosis*	Slow	Pulmonary, lymphadenitis, gastrointestinal, wasting
M. chelonae	Rapid	Skin, soft tissue, bone
M. fortuitum	Rapid	Skin, soft tissue, bone
M. kansasii	Slow	Pulmonary
M. leprae	Slow	Skin, peripheral nerve
M. malmoense	Slow	Pulmonary, lymphadenitis, skin and soft tissue
M. marinum	Slow	Skin, soft tissue, bone
M. scrofulaceum	Slow	Lymphadenitis, skin
M. xenopi	Slow	Pulmonary, lymphadenitis
M. ulcerans	Slow	Skin, soft tissue (Buruli's ulcer)

*Rapid = growth <1 week; slow = growth >1 week.

In HIV unaffected individuals, pulmonary infections with NTM traditionally had been found in older males. However, it has been found that bronchiectatic MAC disease may also present in older, thin females without prior pulmonary disease (Lady Windermere syndrome), sometimes in the presence of pectus excavatum, mitral valve prolapse, or scoliosis.[48]

In HIV-infected individuals, NTM disease usually manifests when the host's CD4/T-lymphocyte cell counts are less than 50 cells/mL and often presents as a disseminated, multiorgan infection, commonly from *M. avium*. Acquisition of the NTM is usually through the GI or respiratory tracts; symptoms are nonspecific and include fever, night sweats, weight loss, anorexia, and diarrhea. Disseminated disease has also been reported with *M. intracellulare*, *M. simiae*, *M. marinum*, *M. xenopi*, and *M. abscessus*.

The diagnosis of pulmonary NTM disease is based on a combination of clinical and laboratory criteria[48]:

1. Symptoms and findings on imaging studies (chest radiograph or high-resolution CT scan) consistent with the diagnosis,
2. Exclusion of other conditions with a similar presentation, such as TB, and
3. Either multiple positive sputum cultures of the NTM species, a positive culture from a bronchial wash or lavage, or a biopsy specimen with typical histological features and a positive culture result from either the biopsy specimen or sputum.

Lymphatic disease is the most common NTM presentation in children and rarely affects immunocompetent adults. The majority of cases are due to MAC, and sites are usually unilateral

in cervical, submandibular, submaxillary, or preauricular lymph nodes. The diagnosis may be made by lymph node biopsy and specimen culture. A negative skin test response (<10 mm) may be helpful. Treatment may depend on the particular species of NTM, but localized disease in immunocompetent individuals may include surgical excision of the lymph node.

Skin, soft tissue, and bone disease, most commonly caused by *M. fortuitum*, *M. abscessus*, *M. chelonae*, *M. marinum*, or *M. ulcerans*, usually occurs through penetration, such as in puncture wounds, traumatic injuries, surgical wounds or injection, or skin trauma. For example, tenosynovitis of the hand, commonly from *M. marinum*, may occur in those cleaning aquariums (Color Plate 9-79). Chronic infections may occur in tendons, joints, and bones. In addition to antibiotics, surgical intervention may be indicated.

M. ulcerans is the agent causing Buruli's ulcer, which is an increasing cause of morbidity and disability in many parts of the world, especially West Africa.[49] In animals, natural infections with *M. ulcerans* have been observed in koalas, ringtail possums, and an alpaca.[50]

In animals, *M. paratuberculosis* is the causative agent of Johne's disease (Figure 9-156). This is a progressive infection affecting ruminants, causing GI symptoms such as diarrhea and wasting, and is an important cause of economic losses in cattle. *M. paratuberculosis* also has been postulated as a cause of Crohn's disease in humans.

Avian mycobacteriosis (avian TB) in birds may be caused by several species of NTM, usually of the MAC or *M. genavense*, which are environmentally ubiquitous. These organisms may infect any bird (though uncommon in grey-cheeked parakeets), but is more common in older or immunosuppressed birds (Color Plate 9-80 and Figure 9-157).

Avian TB usually presents as a chronic disease involving the GI tract and liver; signs include wasting despite a good appetite and loose droppings. Primary respiratory signs are uncommon. Rarely, tubercles may be seen on the face and oral cavity of infected birds.[51] The diagnosis of avian TB usually has been made by culture of the organism, although adequate culture specimens may be difficult to obtain. The
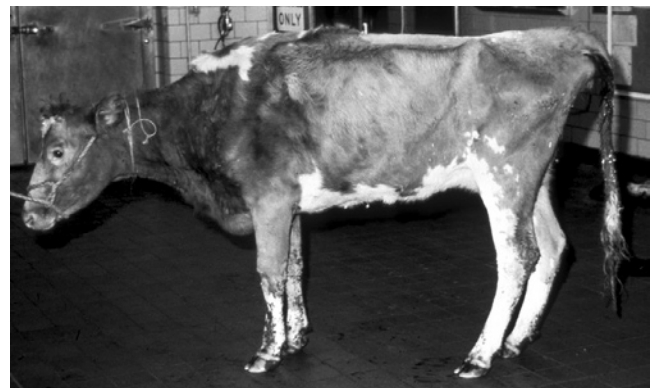

Figure 9-156 ▪ Granulomatous enteritis, Johne's disease (*Mycobacterium avium* spp. paratuberculosis) in a cow. There is chronic wasting and diarrhea in this 18-month-old heifer. The age at which this cow showed clinical signs is not typical of the disease. Signs usually occur 2 or more years after initial infection. (From McGavin MD, Zachary JF: *Pathologic basis of veterinary disease*, ed 4, St Louis, 2007, Mosby Elsevier. Courtesy College of Veterinary Medicine, Cornell University.)
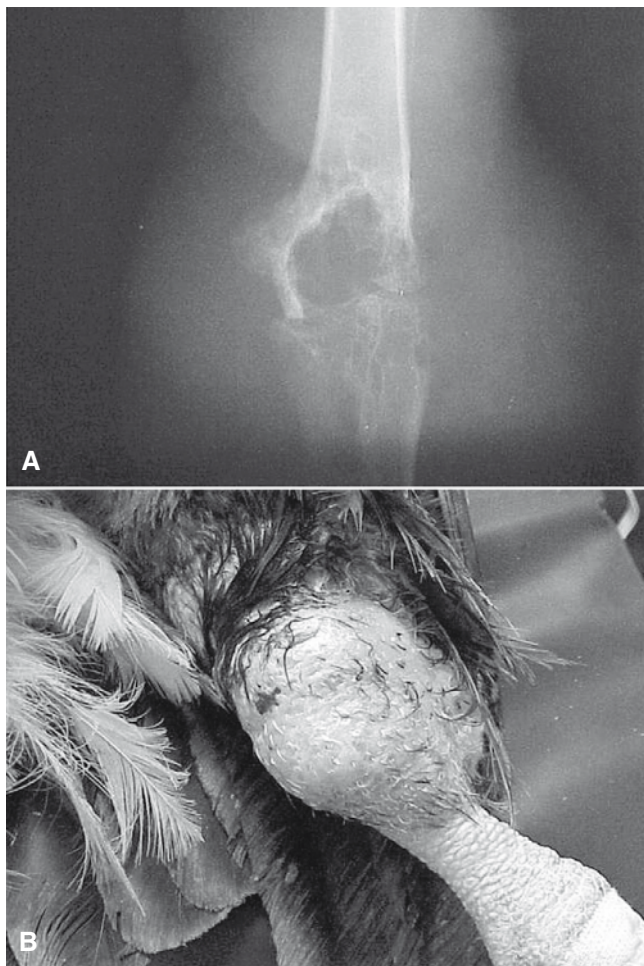
Figure 9-157 ■ **A,** *Mycobacterium avium* is an important pathogen of wild birds. This bald eagle presented with systemic lesions. **B,** The most notable sign was the classic distal tibiotarsal osteomyelitis. (From Mitchell M, Tully TN Jr: *Manual of exotic pet practice*, St Louis, 2008, Saunders Elsevier.)

finding of mycobacterial organisms in histology associated with inflammatory cells and the clinical presentation have been used to make a presumptive diagnosis. PCR testing is available, although the results must be interpreted carefully.[52] A positive result means that there are mycobacteria present but does not necessarily mean that it is the cause of disease. Most birds with avian TB either succumb to the disease or are euthanized. In some areas it is a reportable avian disease.

Other than in birds, MAC infection in mammals is sporadic and not considered transmissible. However, disseminated disease has been reported in captive, nondomestic hoofed animals and in immunosuppressed dogs and cats.[53]

M. marinum may commonly be found in marine animals and water. It can be transmitted directly from fish or marine animals to humans; it may indirectly be transmitted through water or contaminated equipment, such as aquariums (see above). Infection in ecothermic fish may present as a systemic disease with internal tuberculomas, anorexia, weight loss, skin defects, spinal deformities, abdominal distention, and exophthalmia. The prognosis in fish is poor; those affected are usually killed and removed from the environment, as infection may be transmitted if the fish are cannibalized.

M. leprae is the causative agent of leprosy (Hansen's disease) in humans, a chronic, granulomatous disease primarily affecting the skin and peripheral nerves. Leprosy has also been reported in wild armadillos and nonhuman primates. *M. lepraemurium* is the etiologic agent of murine leprosy, a disease primarily affecting the skin and viscera of rats and mice.[54]

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TULAREMIA

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Tularemia (ICD-10 A21)

Other names in humans: rabbit fever, Francis disease, deer-fly fever, Ohara's disease, market men's disease

Other names in animals: rabbit fever, deerfly fever

Francisella tularensis causes an acute febrile illness in humans and other animals that can be fatal. The incidence of tularemia has decreased in the United States since the first half of the twentieth century.[1] However, sporadic outbreaks continue to occur, and the disease has emerged in regions where it previously had not been recognized. Moreover, its widespread occurrence in wildlife and arthropod vectors, its ability to persist in water and soils, and its high infectiousness for both humans and domestic animals make it both a high-priority biological terrorism agent as well as a zoonotic pathogen with potential to cause significant health effects in human and animal populations.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Provide epidemiological analysis of this reportable disease.
- Educate the public to avoid tick, fly, and mosquito bites by using appropriate clothing and repellents.
- Educate hunters to use puncture-resistant gloves when skinning or handling game, especially rabbits, and to cook wild meat thoroughly.
- The CDC recommends that laboratory personnel be alerted when tularemia is suspected. Diagnostic

procedures involving tularemia should be performed in at least biosafety level 2 conditions. Examining suspected cultures should be done in a biological safety cabinet. Procedures that could produce aerosols or droplets require biosafety level 3 conditions.[2]

· Disinfect with 1% sodium hypochlorite, 70% ethanol, and glutaraldehyde.

· Consider the possibility of bioterrorism in the event of a cluster of unexplained cases.

Human Health Clinicians

· Report disease to public health authorities using the case definition; see http://www.cdc.gov/ncphi/disss/nndss/casedef/tularemia_current.htm.

· Consider the diagnosis in persons presenting with acute onset of fever and exposure to ticks or animals.

· Inquire about occupational risk factors for infection and ensure that workers at risk take precautions.

· Ensure that any laboratory workers handling strains of tularemia virulent to humans are using biosafety level 3 precautions.[3]

· Provide PEP following aerosol exposure.

· A vaccine for tularemia is under review by the FDA but is not currently available in the United States.[4]

Veterinary Clinicians

· In many states tularemia in horses is a reportable disease to the state veterinarian. Disease in cats and dogs may be reportable to public health authorities.

· In endemic areas, counsel owners to neuter cats to prevent roaming and keep cats indoors.

· Treat dogs, cats, and horses for ectoparasites.

· Ensure policies are in place to isolate suspected cases and for veterinary staff to use protective equipment and extreme care in handling infected animals, carcasses, or tissues.

· Treat early if tularemia is suspected; otherwise, prognosis is poor.

Agent

Francisella tularensis is a small, gram-negative intracellular coccobacillus. Two major subspecies are recognized with different biochemical and pathological characteristics: *F. tularensis tularensis* and *F. tularensis holarctica*. *F. tularensis* subspecies *tularensis* (Jellison type A) is considered to have higher virulence, with human case fatality rates between 5% and 15% without treatment and a median lethal dose (LD_{50}) in rabbits of 1 to 10 organisms. *F. tularensis* subspecies *holarctica* (Jellison type B) has a lower infectivity (LD_{50} >10^6 organisms in rabbits) and rarely causes human fatalities.[5] Recently type A isolates in the United States have been further divided, using molecular techniques, into type A-East and type A-West, with type A-West less virulent than either type A-East or type B.[6] Viable organisms can be found for months in fomites or the carcasses or hides of infected animals and years in frozen infected meat. The organism can be

disinfected with 1% hypochlorite, 70% ethanol, glutaraldehyde, or formaldehyde or inactivated by moist heat (121°C for at least 15 minutes) and dry heat (160-170°C for at least 1 hour).[7]

Geographical Occurrence

Tularemia is a disease of the Northern Hemisphere. Historically, the highest prevalence has been recorded in the United States and Russia. However, in both countries the prevalence has declined significantly since World War II. In the United States, the incidence peaked in 1939 with 2291 reported cases; in recent decades the average number of U.S. cases has been less than 200 annually.[1] Most cases occur in the south-central and western states, including Missouri, Alaska, Oklahoma, South Dakota, Tennessee, Kansas, Colorado, Illinois, Utah, and Montana.[8] The two major pathogenic strains vary in their geographical distribution. *F.* subspecies *tularensis* is primarily confined to North America, although isolation of strains resembling *F. tularensis* subspecies *tularensis* has recently been reported in Europe.[9] *F. tularensis holarctica* is also found in North America but to a lesser extent. By contrast, it is the predominant strain in Europe and Northern Asia. A third strain, *F. tularensis* subspecies *mediasiatica,* is found in central Asia.

Groups at Risk

In the United States, higher attack rates occur in children aged 5 to 9 years and individuals 75 years or older. Native Americans/Alaskan natives have an incidence of 0.5 per 100,000, 10 times the rate in whites (0.04/100,000). It is thought that the higher rates in children reflect exposure risk due to tick and other insect bites, whereas the increased risk in Native Americans may be related to increased exposure. High rates of infection in ticks and dogs have been found in reservations reporting human outbreaks.[1]

Other risk groups include farmers, landscapers (especially those engaged in mowing lawns[10]), and hunters who may encounter carcasses of infected rabbits or other animals. Cat ownership has been reported as a risk factor for infection in areas experiencing outbreaks.[11] Veterinarians and wildlife rehabilitators may be at risk through handling sick animals. Laboratory workers are also at risk because of the infectiousness of the organism.

Hosts, Reservoir Species, Vectors

Tularemia is found in more than 250 species of mammal, birds, reptiles, and fish.[8] Aquatic animals have developed tularemia after being immersed in contaminated water Different species vary in their susceptibility to the disease. In the United States, cottontail rabbits (*Sylvilagus* species) as well as jackrabbits, beaver, moles, squirrels, muskrat, meadow voles, and sheep are prone to the disease, which is often fatal.

Cats are at increased risk because of their predatory habits. A serological survey found evidence of past infection in 24% of cats tested in Connecticut and New York, suggesting that the disease in cats may be more common than often recognized.[12]

Tularemia is found in a number of vector species, including several species of tick, deer flies, mites, lice, midges, fleas, bedbugs, and mosquitoes. Vector-transmitted infections are believed to account for the majority of human and other animal cases in the United States. Recognized vectors in the United States include the wood tick *(Dermacentor andersoni),* dog tick *(D. variabilis),* lone star tick *(Amblystoma americanum),* and the deer fly *(Chrysops discalis).*[8] Flies can carry *Francisella* for 2 weeks and ticks may be infected throughout their lifespan.

Mode of Transmission and Life Cycle

Animal-to-animal and animal-to-human transmission of tularemia appears to take place through a variety of mechanisms, including direct inoculation through a bite from an infected arthropod vector, a bite or scratch or conjunctival contact from an infected animal, inhalation of aerosols containing organisms, and ingestion of contaminated food or water (Figure 9-158). Human-to-human transmission has not been reported. The mode of transmission helps determine the clinical form of the disease.

In the United States, the most common form of the disease is the ulceroglandular type, which develops after a vector bite (usually a tick or fly) and consists of an ulcer at the site of the bite with associated lymphadenopathy and fever. Direct handling of infected carcasses (especially rabbits) can also result in this form of infection. Less commonly, the inhalation of organisms results in primary pneumonic tularemia. Contact with mucous membranes of a susceptible host causes the oculoglandular form of the disease. Ingestion of contaminated meat or water can cause a typhoidal form of the disease characterized by fever and nonspecific GI symptoms, including diarrhea.[13]

Although rare, there are cases of humans developing infection from contact with infected cats and dogs. Exposure risk factors include cat bites[14] and being licked by an infected dog.[15]

Environmental Risk Factors

F. tularensis can survive for months in water and sediment. A number of human outbreaks have occurred next to bodies of water, including one associated with crayfish fishing.[16]

In an outbreak of pneumonic tularemia in Martha's Vineyard, skunks and raccoons were found to frequently be seroreactive, raising the possibility of peridomestic environmental contamination by feces; however, this has not been confirmed as the source of illness.[17] Another environmental factor is the changing conditions that can lead to increases in rodent populations; outbreaks have been associated with increases in populations of rodents. Intentional introduction of game animals such as hares into new geographical areas for hunting has lead to outbreaks in Spain, where it had not been previously reported.[18]

Disease in Humans

Tularemia causes an acute febrile disease that usually begins 3 to 5 days after exposure. Although most cases are charac-

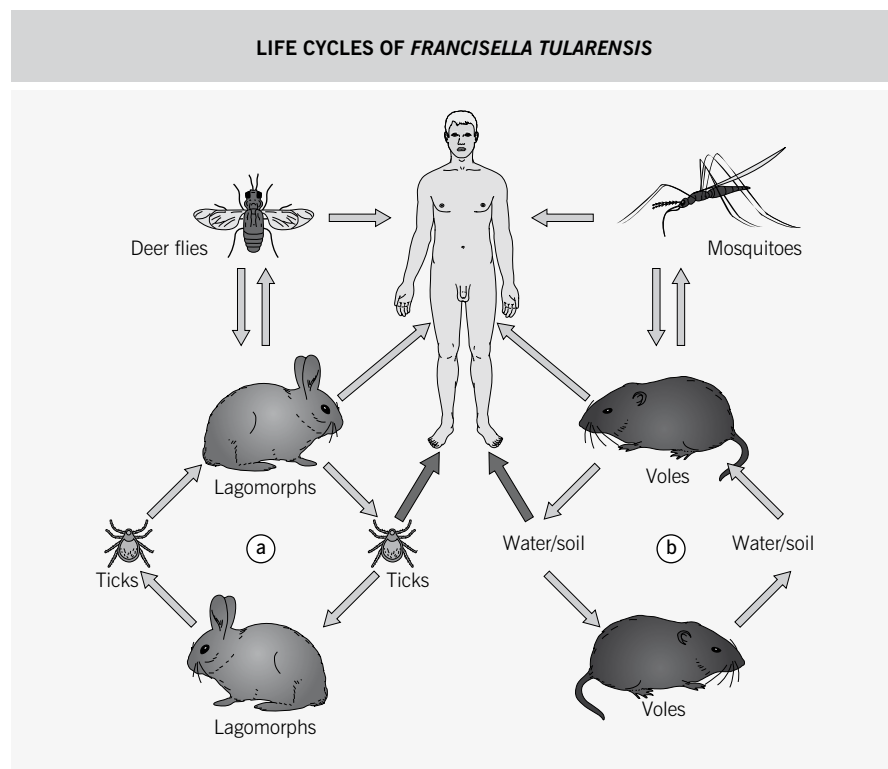**LIFE CYCLES OF *FRANCISELLA TULARENSIS***

Figure 9-158 ■ Life cycles of *Francisella tularensis.* (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, Philadelphia, 2004, Mosby Elsevier.)

Figure 9-159 ■ This Vermont muskrat trapper contracted tularemia, which manifested as a cutaneous lesion on his left lateral forehead. (From Centers for Disease Control and Prevention Public Health Image Library, Atlanta, Ga.)

terized by the abrupt onset of fever, chills, fatigue, myalgia, headache, and nausea, several distinct forms of the disease are related to the mode of transmission and the virulence of the organism. Infection caused *F. tularensis* subspecies *tularensis* may progress to septicemia, with disseminated intravascular coagulation, acute respiratory distress syndrome, CNS involvement, and multiorgan failure. Disease related to *F. tularensis* subspecies *holarctica* is more likely to produce mild symptoms with a low case fatality rate.

Most cases (87%)[19] present as *ulceroglandular tularemia*, resulting from insect bites or direct contact with an infected carcass (Figure 9-159 and Color Plate 9-81). One of the first symptoms is lymphadenopathy localized in the area where the bite or scratch occurred. A painful papule develops either simultaneously or within several days at the site of the initial skin entry. This papule then ulcerates, taking several weeks to heal.[5] The lymphadenopathy may also suppurate and become ulcerative (Color Plate 9-82). Rarely, if there is contact with conjunctival membranes, *oculoglandular tularemia* develops, with purulent conjunctivitis and lymphadenopathy. *Glandular tularemia* resembles the ulceroglandular form but without skin lesions.[19]

Primary pneumonic tularemia results from inhalation of infected aerosols and manifests as pneumonitis and bronchiolitis, which may lead to respiratory failure. Pneumonic tularemia may also develop as a complication of other forms and is associated with a higher mortality rate.[19]

The *typhoidal* form of tularemia is considered rare, is caused by ingestion of contaminated food or water, and may be difficult to diagnose. Symptoms can include fever, gastroenteritis, septicemia, and pneumonia. Ingestion may also lead to *oropharyngeal tularemia* with throat pain, prominent pharyngitis, oral ulcers, and enlargement of cervical lymph nodes.

Disease in Animals

Susceptibility to *F. tularensis* infection varies among animal species. Rabbits and many rodents develop fatal disease. Sheep also have high mortality rates.

Cats can develop an acute febrile syndrome caused by tularemia that can be fatal (Color Plate 9-83). Ulceroglandular disease in cats has also been reported.[20] Dogs appear to be more resistant and likely to develop asymptomatic infection. However, fever, anorexia, and lethargy have been reported in a dog that ate an infected rabbit.[21]

Horses can develop a febrile infection associated with impaired coordination and depression.[22] Cattle appear to be resistant. Table 9-73 compares clinical presentations of tularemia in humans and other animals.

Diagnosis

Diagnosis in humans is usually based on clinical signs and confirmed by serological studies showing at least a fourfold rise in titer that occurs 2 weeks after the onset of illness. A direct immunofluorescence test and/or PCR test may be available for rapid diagnosis.

Culture of body fluids should be performed only in reference laboratories because of risk of infection to laboratory personnel. Lymph nodes should not be biopsied unless antibiotics have already been started because of the risk of inducing bacteremia.[5]

In other animals, a direct antibody or IFA assay (Color Plate 9-84) is considered the most rapid and accurate means of diagnosis[15]; an immunohistochemical analysis for formalin-fixed tissue has also been developed. Serology is used if the animal survives, with a fourfold titer difference between acute and convalescent titers confirming infection. Culture of the bacterium can be performed but poses a health risk for laboratory personnel.

Treatment

Antibiotics are the mainstay of therapy. Isolation of patients and prophylactic treatment of contacts of human patient are not necessary because human-to-human transmission has not been observed. For individuals who have had high-risk exposures to infected animals or other sources of the organism, prophylactic antibiotics are indicated as shown in Table 9-74. (NOTE: tetracycline and chloramphenicol are bacteriostatic and have been associated with relapses in humans.)

Little is known about effective treatment regimens in animals because the disease is often fatal before treatment begins. However, recommended antibiotic regimens are shown in Table 9-74. An important part of animal treatment is isolation of the animal and protection of veterinary staff, including wearing of gowns, gloves, and face masks, including eye protection, when handling a suspected case.[15]

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Table 9-73 ▪ Tularemia: Comparative Clinical Presentations in Humans and Other Animals

Species	Risk Factors	Incubation Period	Clinical Manifestations	Laboratory Findings
Humans	Children, Native Americans, hunters, landscapers, others with wildlife contact	Usually 3-5 days (range, 1-14)[5]	Fever, lymphadenopathy, fatigue, pneumonia Ulceroglandular form: ulcer at site of entry Glandular form Primary pneumonic form Oropharyngeal form Typhoidal form	Positive serology, direct immunofluorescence
Cats, dogs	Outdoor/hunting cats Tick and other insect bites Dogs more resistant than cats	2-7 days[15]	Fever, anorexia, lethargy, lymphadenopathy, hepatosplenomegaly Ulcers in mouth, pseudomembrane on tongue[15] Mucous membranes icteric	Pan leukopenia, leukocytosis, elevated liver function tests DFA of tissues, serology, blood culture
Sheep	Tick exposures	1-10 days[8]	Fever, septicemia, rigid gait, diarrhea, urination, respiratory distress, death[22]	
Swine	Tick exposures	1-10 days[8]	*Adults fairly resistant:* fever, shortness of breath, depression[22] *Young animals:* lack of coordination, depression, anorexia, neurological signs	
Rabbits	Very susceptible	1-10 days[8]	Depression, anorexia, ataxia, roughened coat, tendency to huddle, weakness, fever, ulcers, abscesses at site of infection, dyspnea, swelling of regional lymph nodes, sudden death Usually not recognized until dead or dying	
Horses	Tick exposure (rare)	1-10 days[8]	Lack of coordination, fever, depression, dyspnea	

DFA, Direct immunofluorescence antibody.

Table 9-74 ▪ Antibiotic Treatment of Tularemia Infection in Humans and Other Animals

Species	Primary Treatment	Alternative Treatment
Humans (adult)		
Inhalational	Streptomycin 15 mg/kg IV bid *or* gentamicin 5 mg/kg IV qd × 10 days	Doxycycline 100 mg PO or IV bid × 14-21 days *or* ciprofloxacin 400 mg IV (or 750 mg PO) bid × 14-21 days[24]
Typhoidal	Gentamicin or tobramycin 5 mg/kg/day divided q8h IV × 7-14 days	Add chloramphenicol if evidence of meningitis[24]
Postexposure prophylaxis: adult	Doxycycline 100 mg PO bid × 14 days	Ciprofloxacin 500 mg PO bid × 14 days
Cats, dogs (early treatment is critical)	Amoxicillin 20 mg/kg IM or SC q12h or PO q8h *PLUS* gentamicin 4.4 mg/kg IM or SC q12h once, then q24h thereafter until clinical response or until 7 days	Enrofloxacin 10-15 mg/kg PO, IM, IV, or SC q12h[15]
Sheep	Streptomycin or gentamicin	Chloramphenicol 25 mg/kg IV qid *or* tetracyclines[8]

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WEST NILE VIRUS AND OTHER ARBOVIRUS INFECTIONS

Carina Blackmore

West Nile virus infection (ICD-10 A92.3)

Other names in humans: West Nile fever, West Nile meningitis, West Nile encephalitis, West Nile poliomyelitis

Other names in animals: West Nile virus infection

West Nile virus (WNV) was first isolated from a febrile woman in Uganda in 1937.[1] The first human disease outbreak occurred 20 years later in Israel. The virus was first detected in the Americas in 1999 by a veterinary pathologist when a flavivirus was identified as the cause of an apparent zoonotic encephalitis outbreak in humans and corvid birds (e.g., crows and jays) in Queens, New York. WNV has since become the most important cause of mosquito-borne disease in North America. It spread across the 48 continental United States in 6 years, and more than 27,000 human cases and 25,000 horse cases of WNV disease were reported during the period 1999 to 2007. Outbreaks of human or equine WNV encephalitis have also occurred in southern Europe, Israel, the Democratic Republic of the Congo, and Russia. WNV is an example of a disease where tracking sentinel cases in birds,[2] horses, dogs,[3] and other animals, as well as WNV positive pools of mosquitoes, has proved useful for efforts aimed at early detection and prevention of human cases.

Several zoonotic arthropod-borne (arboviral) diseases are known to circulate within the United States, including St. Louis encephalitis (SLE), Eastern equine encephalitis (EEE), La Crosse encephalitis (LAC) and Western equine encephalitis (WEE). These arboviruses may have different vector and vertebrate hosts than WNV but many of the guidances discussed below are relevant for prevention of and control of them all. They are also relevant for potentially emerging zoonotic arboviruses such as Rift Valley Fever virus.

Key Points for Clinicians and Public Health Professionals

Public Health Professionals

- Recommend to the public:
  - Do not go outdoors at dusk and dawn when mosquitoes are most active.
  - Empty containers and drain stagnant waters where mosquitoes lay their eggs.
  - Install or repair window and door screens.
  - Dress so skin is covered with clothing.
  - Stock ornamental ponds with mosquito-eating fish.
  - Maintain pools.
  - Protect bare skin and clothing with a mosquito repellent. Make certain the repellent is used according to its label. Do not use repellents over cuts, wounds, or irritated skin. Do not use repellent under clothing.
- DEET (*N,N*-diethyl-3-methylbenzamide)[4] and picaridin[5] are effective repellents registered for skin application by the EPA. Depending on the duration of protection desired, products containing 4.75% DEET provide roughly 90 minutes' effectiveness; products containing 23.8% DEET provide an average of 5 hours of protection.[6]
- Among plant-based repellents registered with the EPA, oil of lemon eucalyptus provides longer-lasting protection than others, with an efficacy similar to a

repellent with low concentrations of DEET. Repellents can be reapplied according to the manufacturer's instructions.

- Sunscreen and insect repellent can be applied simultaneously. However, it is not recommended to use a product combining sunscreen and repellents as sunscreen often needs to be applied more frequently and repeated application may increase the toxic effects of the repellent.
- Permethrin, a pyrethroid product, is an effective repellent registered for application on clothing, camping gear, or mosquito nets.
- Safety precautions when using repellents on children:
  - Keep repellents out of the reach of children.
  - Do not allow young children to apply insect repellent to themselves; have an adult do it for them.
  - Apply the repellent to your own hands and then rub them on the child. Avoid children's eyes and mouth and use it sparingly around their ears.
  - Do not apply repellent to children's hands as children may tend to put their hands in their mouths.
  - Wash treated skin with soap and water after returning indoors and wash treated clothing.
  - The American Academy of Pediatrics does not recommend repellents be used on children younger than 2 months. Instead, they recommend the use of mosquito netting over infant carriers. Oil of lemon eucalyptus products should not be used on children younger than 3 years.
- Determine and implement the most appropriate surveillance methods for WNV risk in your region, considering possible use of mosquito, bird, or mammal sentinel information, as well as climate tracking (Color Plates 9-85 and 9-86).

Human Health Clinicians

- In suspected cases, submit serum and/or CSF for WNV antibody testing.
- Monitor public health surveillance on human WNV disease in the local area, including surveillance of sentinel animals, to estimate current human health risk.
- Counsel all patients, especially adults older than 50 years and families with infants, to avoid being bitten by mosquitoes, including the appropriate use of repellents and mosquito netting.
- Report cases to the health department if required in the state per recommended case definition.

Veterinary Clinicians

- Advise horse owners on how to prevent equine WNV disease. Horses should be protected from mosquito bites. This can be done by eliminating mosquito breeding sites, providing screened housing, and applying insect repellents.
- Vaccinate horses against WNV disease. There are three licensed WNV vaccines currently available: an inactivated whole virus vaccine, a live recombinant canary pox vector vaccine, and a modified live chimera vaccine. The American Association of Equine Practitioners

provides the following guidance on WNV vaccination of horses[7]: Primary vaccination of previously unvaccinated horses with either the inactivated or canary pox vector vaccine involves administration of 2 doses of vaccine 4 to 6 weeks apart followed by revaccination at a 12-month interval. Label instructions for the modified live chimera vaccine recommend a single injection followed by a 12-month revaccination interval. More frequent boosters may be warranted for juvenile (<5 years) or geriatric (>15 years) horses. Although the licensed WNV vaccines are currently not labeled for administration to pregnant mares, many veterinary practitioners do administer them to pregnant mares. Booster vaccination of pregnant mares 4 to 6 weeks before foaling provides passive, colostral protection to their foals. To avoid interference from colostral antibodies, primary vaccination of foals from vaccinated mares should be started at 4 to 6 months of age. Foals should receive a third dose in the spring of the year following their birth. Foals of unvaccinated mares should ideally receive two doses of vaccine before the mosquito-borne disease season starting at 3 months of age. The modified live flavivirus chimera vaccine is labeled for foals 5 months or older. A single dose should be administered followed by a second dose at 10 to 12 months of age (before the next WNV season).

- Prevent dogs and cats from eating birds and other wildlife.
- Maintain barrier precautions when performing necropsies, particularly on birds.
- Related flaviviruses are destroyed by 1% sodium hypochlorite, 2% glutaraldehyde, and 70% ethanol.[8]

Agent

WNV is part of the Flaviviridae family in the genus *Flavivirus* (Figure 9-160). Flaviviruses are small (40 to 60 nm), lipid-enveloped RNA viruses containing a single positive-strand genomic RNA. The lipid surface contains the viral envelope (E) and membrane (M) "spike" proteins. WNV and SLE virus are closely related and both are members of the
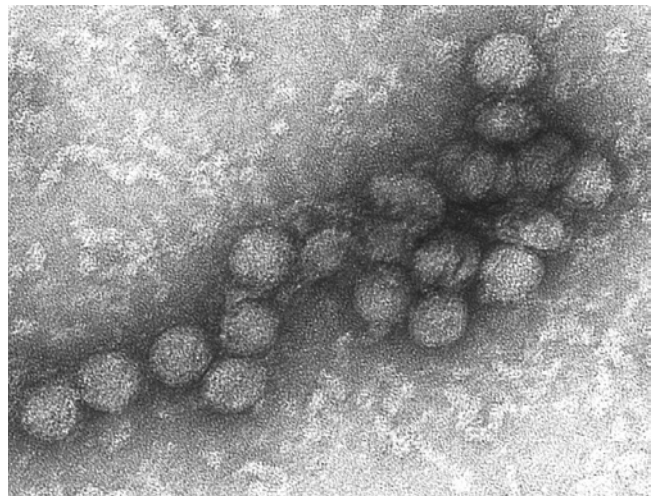

Figure 9-160 ▪ Electron microscopy of the West Nile virus. (From Auerbach PS: *Wilderness medicine*, ed 5, Philadelphia, 2007, Mosby Elsevier.)

Japanese encephalitis antigenic serocomplex.[1] More distantly related mosquito-borne flaviviruses in the Americas include yellow fever and Dengue virus.

Geographical Occurrence

WNV was first identified in Uganda in 1937. It is now endemic in parts of Africa, Europe, Australia, and Asia as well as North, Central, and South America.[9,10]

Groups at Risk

WNV is transmitted by mosquito bite, and persons in all age groups are at risk of infection. In areas where WNV is hyperendemic, it is a mild, common childhood illness.[11] In industrialized temperate areas the incidence of neuroinvasive WNV disease and death increases in those who are immunosuppressed or 50 years and older.[11,12] The risk for WNV meningitis and encephalitis is also slightly higher among males than females.

Hosts, Reservoir Species, Vectors

WNV is a mosquito-borne virus. The enzootic cycle involves transmission of the virus among infected *Culex* mosquitoes and wild birds (Figure 9-161). Many bird species can become infected by WNV, although only a small proportion are likely to be important reservoir hosts. Passerine birds (crows, jays, finches, grackles, sparrows) are thought to play a role in the WNV transmission cycle. They are common, widespread, and develop a high and prolonged viremia,[13] all important features for a vertebrate reservoir host. Humans, horses, and other mammals are incidental hosts of the virus.

Mode of Transmission and Life Cycle

WNV is maintained in nature by mosquitoes and wild birds (Figure 9-162). The overwintering mechanisms of the virus are not fully understood; however, overwintering adult mosquitoes are thought to play a role.[14] Human and other mammals are incidental hosts of the virus. Non-mosquito-borne transmission such as transplacental infection, breast-feeding, blood transfusion, and organ transplantation have also been documented.[15] Fecal-oral transmission has been reported among animals including alligators, cats, some raptors, hamsters, and golden crows.[16]

Figure 9-161   ■   *Culex* mosquito. (From Florida Medical Entomology Laboratory, Michelle Cutwa-Francis, photographer.)

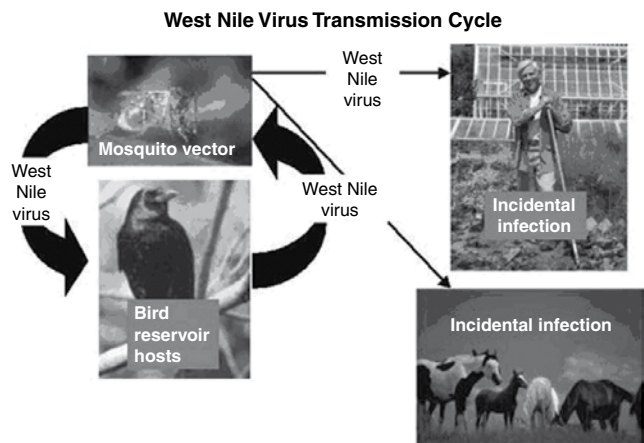**West Nile Virus Transmission Cycle**

Figure 9-162   ■   West Nile virus transmission cycle. (From Centers for Disease Control and Prevention: *Flowchart: West Nile virus transmission cycle.* http://www.cdc.gov/ncidod/dvbid/westnile/cycle.htm.)

Environmental Risk Factors

Virus amplification and transmission are favored by warm temperatures, and the peak virus activity occurs in the late summer months. Different vectors prefer different breeding habitats. The *Culex pipiens* species breed in stagnant pools of groundwater, artificial containers, catch basins, or sewage seepage. They prefer to breed in highly organic (polluted) water. *Culex tarsalis*, the most important WNV vector in the western United States, tolerates a wide range of habitats but prefers permanent or semipermanent seepage areas and surface pools associated with irrigated pastures. *Culex nigripalpus,* a principle WNV vector in the Southeast, is a floodwater mosquito.

Disease in Humans

Most individuals infected with WNV (80%) remain asymptomatic.[17] The clinical presentation ranges from a mild non-neuroinvasive fever illness to encephalitis, coma, and death (Table 9-75). It is estimated that fewer than 1% of infected persons develop severe neurological disease. Typical symptoms of West Nile fever include fatigue, fever, headache, and muscle weakness. Half of the persons interviewed in a survey among West Nile fever patients in Chicago also had difficulty concentrating.[18] More severe clinical syndromes include aseptic meningitis, myelitis, polyradiculitis, and encephalitis. Patients often present with a prodrome of fever, headache, and other nonspecific symptoms. Many develop movement disorders such as severe tremors and parkinsonism.[19]

Disease in Animals

Horses infected with WNV may develop fever, depression or apprehension, stupor, behavioral changes, intermittent lameness, ataxia, caudal paralysis, droopy lip, teeth grinding, muscle twitching, tremors, difficulty rising, recumbency, convulsions, and death.[20,21] In one study, approximately 33% of horses with clinical signs of WNV infection died from the disease.

Clinical signs of WNV infection in birds vary greatly among species. Many avian species develop clinically

Table 9-75 ▪ West Nile Virus Infection: Comparative Clinical Presentations in Humans and Other Animals				
Species	**Risk Factors**	**Incubation Period**	**Clinical Manifestations**	**Laboratory Findings**
Humans	Mosquito exposure, age, immunosuppression after organ transplantation, and male gender are risk factors for severe illness[19] Other risk factors include receiving blood transfusions or organ donations, and occupational exposure Infants may become infected by maternal infection during pregnancy or breastfeeding	3-14 days[18]	Fever, headache, muscle pain, weakness, fatigue, ocular pain, malaise, anorexia, maculopapular or morbilliform rash on neck, trunk, and extremities 5-12 days after onset[18,19] *Neuroinvasive disease:* ataxia and extrapyramidal signs, optic neuritis, seizures, tremor, myoclonus, parkinsonism and altered mental status[12,27] Rash, polyradiculitis, and acute asymmetric poliomyelitis like flaccid paralysis are seen in a small number of patients.[19,28]	*CSF:* Specific WNV IgM antibodies, lymphocytic pleocytosis, elevated protein, normal glucose *Blood:* Specific WNV IgM or IgM and IgG antibodies in serum Peripheral blood total leukocyte count normal or elevated, anemia, and lymphocytopenia Brain magnetic resonance imaging results often normal Signal abnormalities may be detected in the basal ganglia, thalamus, and brainstem of patients with encephalitis and in the anterior spinal cord in patients with flaccid paralysis[19] Virus detection in CSF or tissues is also possible
Horses	Mosquito exposure	3-15 days	Fever, depression or apprehension, stupor, behavioral changes, intermittent lameness, knuckling over at the metacarpo- or metatarsophalangeal joints, ataxia, caudal paralysis, droopy lip, teeth grinding, muscle twitching, fasciculations and tremors, difficulty rising, recumbency, convulsions, blindness, and colic or death[16,20,21]	Fourfold rise in WNV serum antibody, positive IgM ELISA antibody test in serum or CSF Antigen detection in brain tissue using viral culture, PCR, or immunohistochemistry
Birds	Mosquito exposure Possible contact with other birds or their excretions Possible exposure from predation on other infected birds/mammals	Unknown	Signs of WNV neurological disease include sudden onset of mild ataxia, abnormal head posture, circling, reclining, quadriparesis, and tremors; nystagmus, seizures, disorientation, signs of depression, anorexia, weight loss, impaired vision, and sudden death may also be present.[16,23]	WNV detection in brain, heart, kidney or liver tissue Fourfold rise in WNV antibody titer Rapid screening tests on oral or cloacal swabs, swabs of organ tissue, or feather pulp
Dogs, cats	Allowed to roam outdoors, stray animals	Unknown[22]	Usually asymptomatic, fever, lethargy reported in cats, encephalitis, arthritis, myocarditis in dogs	Serology, PCR

CSF, Cerebrospinal fluid.

inapparent infections, whereas others become severely ill and succumb to the virus. Signs of WNV neurological disease include sudden onset of mild ataxia, abnormal head posture, circling, reclination, quadriparesis, and tremors. Nystagmus, seizures, disorientation, signs of depression, weight loss, impaired vision, and sudden death may also be present.[9,23] Birds shed virus orally and in their feces, and bird-to-bird transmission has been reported.[9,24] Gross pathology often includes an enlarged, necrotic, and hemorrhaging liver and spleen, myocardial degeneration and inflammation, pericardial lesions, pancreatitis, and chronic adrenalitis.

Dogs and cats appear to be relatively resistant to WNV and generally develop subclinical disease after exposure. Acute encephalitis, polyarthritis, and myocarditis have been reported in dogs.[22] Fever and lethargy have been reported in cats. In addition, WNV has been isolated from the brain of a cat with neurological disease.[25]

Outbreaks of WNV disease with high mortality rates have been seen among farm-raised alligators. The virus appears to spread via fecal-oral transmission in the alligator pens (Color Plates 9-87 and 9-88).

WNV infection has also been documented in bats, a skunk, and a few rodent species.

Diagnosis

Serological tests used to diagnose WNV infection include ELISA and antigen (IgM and IgG) capture ELISA, hemagglutination inhibition, plaque reduction neutralization, and virus neutralization. Virus can also be identified in the CNS and other tissues using virus isolation, PCR, and immunohistochemistry.

For surveillance of WNV in dead birds, public health and partner agencies have used the VecTest antigen-capture assay (Medical Analysis Systems, Camarillo, Calif.),[29] Rapid Analyte Measurement Platform (RAMP) assay (Response Biomedical Corp, Burnaby, British Columbia, Canada),[30] and real-time RT-PCR.

Treatment

There is no specific treatment for WNV infection in either humans or animals. In more severe human cases, intensive supportive care is indicated, such as hospitalization, intravenous fluids, airway management, respiratory support (ventilator), prevention of secondary infections (pneumonia, urinary tract, etc.), and good nursing care. Research trials are under way to identify effective antiviral treatment and vaccines.

Nonspecific immunoglobulin and plasmapheresis should be considered for patients with Guillain-Barré syndrome. The treatment is not indicated for patients with paralysis due to damage of anterior horn cells.[28]

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