Toxoplasmosis

Toxoplasma gondii

Toxoplasma gondii is an obligate intracellular, protozoal pathogen of humans and a variety of animal species. In all hosts, the organism enters a chronic, persistent phase following acute infection, and this persistence leads to the potential for reactivation of clinical disease at a later date (a particularly serious problem in AIDS patients). Toxoplasmosis is one of the best known zoonotic diseases among physicians, veterinarians and the general public, and cats play a critical role in the life cycle and maintenance of the organism in nature. Cats (domestic and non-domestic felids) are, in fact, the only definitive host in which Toxoplasma gondii undergoes sexual reproduction.

- Sexual replication of Toxoplasma gondii occurs in the gut of the cat during the enteroepithelial stage of the life cycle, which takes about 3-10 days. Sexual replication leads to the production of oocysts. The oocysts are passed in the cat’s feces and sporulate in the soil to become infectious. After ingestion by intermediate hosts (rodents, birds, sheep, pigs, [humans]), they cause a systemic infection (asexual replication, initially as rapidly dividing tachyzoites, followed by encystation as bradyzoites). The organism’s life cycle is completed when new cats ingest tissues of the intermediate hosts containing Toxoplasma cysts containing bradyzoites. (Note: cats can also be infected by ingestion of oocysts shed from other cats, but this is a much less efficient method of infection. Only ~20% of cats exposed to oocysts become productively infected, whereas virtually 100% of naïve cats that ingest tissues cysts will become infected and shed oocysts.) When dogs consume cat feces, oocysts may pass through the GI tract into feces, with subsequent mechanical dispersal of the organism, but dogs do not support actual replication of Toxoplasma in their gut.

Humans can be infected with Toxoplasma gondii by one of three routes; the overall role of cats in the epidemiology of human exposure to this organism needs to be viewed from a basis in fact, not fear:

1. Ingestion of sporulated oocysts shed in cat feces
   - It’s critically important to realize that cats generally only shed the organism for 10-14 days following initial infection. At any one time, <1% of cats in the U.S. are shedding Toxoplasma oocysts. However, serologic evidence of prior infection is common in cat populations in the U.S., e.g., 49% of feral cats in Dane County, WI (2003 data, Dr. R.D. Schultz, personal communication); 50% of feral cats and 36% of client-owned cats in a Rhode Island survey; 39% of humane society cats in a Columbus, Ohio survey; 42-68% of cats on swine farms in Iowa and Illinois surveys; 63% of feral cats in North Carolina; and, 31.6% of sick cats nationwide in the U.S.
     -- The risk of reactivation and shedding following intercurrent disease/stress in cats is quite low. Daily oral prednisone at doses <10mg/kg does not appear to cause renewed shedding. Likewise, shedding patterns do not appear to be altered by infections with FeLV or FIV.
Curiously, latently infected cats may shed *Toxoplasma* oocysts for a short period of time after secondary infection with another coccidian parasite, *Isospora felis*.

- It’s also important to understand that **once oocysts are shed in the feces of a cat, they require a period of at least 1-5 days for sporulation before they are infectious** (longer at colder temperatures). Hence, contact with fresh feces is of much less risk than contact with feces in soil or feces left sitting in a litter box for several days.

  -- *T. gondii* has also been isolated from queen’s milk.

- Sporulated oocysts are very resistant in the environment and may remain infectious for over 18 months under favorable conditions.

2. **Ingestion of the bradyzoite form of the organism encysted in meat**

- Despite the role of cats as the definitive host for *Toxoplasma gondii*, multiple studies have shown that consumption of undercooked meats is a more important risk factor for human infection with *Toxoplasma* than is cat ownership. For instance, a large, multi-center study of pregnant woman in Europe with acute *T. gondii* infections (Cook et al., 2000) found that the risk factor most strongly predictive of infection was eating undercooked meats, and up to 63% of infections were attributed to the consumption of undercooked meats. A more recent study (Jones et al. 2009) of adults in the United States also found that elevated risks for infection were associated with eating rare lamb or raw ground beef, eating locally cured/smoked meats and handling raw meat, and consumption of unpasteurized goat’s milk. (Risk was also elevated in this study with ownership of 3 or more kittens; other studies have shown no risk associated with cat ownership.)

  -- Past studies have shown that up to 25% of lamb and pork meat samples in the U.S. may contain the organism. Also 5-22% of U.S. pigs and 53% of goats destined for meat were seropositive for *T. gondii*. The numbers in sheep are less clear, but small-scale studies have indicated that seropositivity in lambs is even higher than in pigs. In contrast, a more recent study (Dubey et al. 2005) of over 6000 meat samples from nearly 700 different stores assayed by pooled feeding trials in cats found less evidence for contamination of retail meats, and only in pork.

  -- Poultry is of minimal risk because poultry meat is often frozen during processing, which kills the organism...and the public is already aware (we hope!) of the need to thoroughly cook poultry in order to kill *Campylobacter* and *Salmonella*.

  -- Infection can also occur from ingestion of undercooked game meat such as venison, bear (very high rates of contamination) and even kangaroo meat!

  -- Infection has also been documented following consumption of unpasteurized goat’s milk and municipal drinking water.

    --- In 1995, 100 people were infected in a multi-person outbreak in Victoria, British Columbia. The only apparent link among these cases was residence in a water district supplying chlorinated but unfiltered water from a single reservoir. Cases occurred following two periods of heavy rain, with run-off into the reservoir and an increase in water turbidity. (This is very reminiscent of the *Cryptosporidium* outbreak in Milwaukee, WI in 1993.) Water-borne toxoplasmosis is an endemic problem in Brazil and has also been reported in India.

3. **Transplacental infection following active replication in the placenta and tachyzoite invasion of the fetus** (See congenital toxoplasmosis below)

**Toxoplasmosis in humans**

* The prevalence of infection in people varies among different populations, e.g., 14.3% of Americans in 1999-2000 or 10.8% of Americans 1999-2004 vs. 87% of French adults. (Do the French eat more undercooked meats?) 1-2% of people in the U.S. seroconvert to *T. gondii* annually.
Symptoms of acute infection in immunocompetent adults

- Less than 20% of infections are clinically evident. When present, clinical signs can include fever, LN’opathy (especially cervical nodes), malaise, myalgias, rash, hepatosplenomegaly and/or chorioretinitis.

--- The disease in immunocompetent individuals is usually self-limiting, but more serious causes of LN’opathy must be ruled out. In addition, there are reports of severe, acute toxoplasmosis, possibly associated with specific strains of the organism (Carme et al., 2002, 2009; Bossi and Bricaire, 2004).

--- A series of studies (as reviewed by Torrey and Yolken, 2003) have suggested that some cases of schizophrenia may be linked to infection with *Toxoplasma gondii*. This conclusion is based primarily on higher rates of seropositivity to *Toxoplasma gondii* in schizophrenia patients compared to controls, and on the fact that alterations in neurotransmitters in animal studies of *Toxoplasma* infection may be similar to those in human schizophrenic patients.

Toxoplasmosis in immunodeficient individuals

* TOXOPLASMOSIS IS A DEVASTATING DISEASE IN IMMUNODEFICIENT HOSTS, AND IS ONE OF THE MAJOR CAUSES OF MORTALITY IN AIDS PATIENTS.

* Infections in AIDS patients are manifest most commonly as encephalitis, leading to headaches, focal seizures or changes in mental status.

- Disease can result from newly acquired, acute infection, but is more commonly due to reactivation of a latent infection in AIDS patients after CD4 counts drop to <100/ul.
- UP TO 50% OF AIDS PATIENTS WHO ARE SEROPOSITIVE (LATENTLY INFECTED) WILL DEVELOP TOXOPLASMA ENCEPHALITIS DURING THE COURSE OF THEIR DISEASE, although death rates due to toxoplasmosis in HIV patients appear to be decreasing in recent years (diagnosis, anti-Toxoplasma therapy, and HAART).

* Acute myocarditis can also occur when the organism is introduced into a seronegative patient with a transplanted heart.

Congenital toxoplasmosis in humans

* Approximately 400-4,000 cases of congenital toxoplasmosis occur in the U.S. annually. This is one of the greatest fears of *Toxoplasma* infection, and is probably the situation in which you will most often be called upon for advice by your clients. Unfortunately, the time for clients to ask questions and learn about the disease is before becoming pregnant, but too often questions arise only after the fact. Hence, the importance of on-going client education as part of YOUR practice/professional activity! (A study published in 2005 [Boyer et al.] found that only 8% of 131 women with confirmed congenital toxoplasmosis were serologically screened during pregnancy.)

* Transmission to the fetus generally only occurs during an acute infection of the mother, not during latency. Therefore, risk of congenital infection of a fetus is restricted to those mothers who are actively infected during pregnancy or within 6-8 weeks immediately prior to conception.

- Confirmation of acute infection during or immediately prior to pregnancy would logically be based upon detection of anti-*Toxoplasma* IgM antibodies in a woman. However, this is not foolproof. A negative IgM titer has a 100% predictive value against recent infection, but a positive titer has a much lower predictive value for recent infection because IgM titers remain elevated for 2-6 months following infection. Using a combination of different IgM assays improves the predictive value for recent infection to 80%.

--- Congenital infection can also be diagnosed by assessing the avidity of IgG antibodies
in the serum of a fetus/neonate (lower in acute infection), detection of anti-Toxoplasma IgM, IgA or IgE antibodies in a fetus/neonate, detection by immunoblotting of specific IgG- or IgM-specific bands in the newborn that are not present in the mother’s serum, and by PCR on amniotic fluid, placental tissues or a variety of fetal tissues.

- **If a woman has IgG Ab to T. gondii, this is evidence of past infection and she should not be at risk for congenital transmission to her baby.** (As long as she is not HIV[+]---women with AIDS may be able to infect their fetuses following reactivation of T. gondii from a latent infection.)
- Overall, estimates suggest that about 50-70% of women in the U.S. are at risk (previously uninfected) for infection with T. gondii during pregnancy.

* **The chance for congenital transmission across the placenta and the severity of ensuing damage to the fetus are related to the gestational age of the fetus at the time of infection:**
  - The greatest risk for transmission across the placenta follows infection during the third trimester; however, the severity of damage is greatest following first trimester infections. (Hence the need for women to know how to avoid infection prior to pregnancy!)
  - Overall, about 1/3 of women who are acutely infected during pregnancy will transmit the organism to their fetus. **Antibiotic therapy during pregnancy can reduce this risk 60-75%.**

* **The effects on the fetus of congenital infection include**
  - fetal death and spontaneous abortion
  - chorioretinitis and blindness
    -- Beyond its occurrence as a congenital infection, ocular toxoplasmosis can also occur following acute infection of children or adults. Ocular toxoplasmosis may be associated with infection with specific strains (type I) of the organism.
  - hydrocephalus >>> psychomotor deficits, seizure disorders, cerebral calcifications, compromise of cognitive functions
  - myelitis and paralysis
  (Note: 85-90% of congenitally-infected children will be asymptomatic at birth, but more than 80% of these children will subsequently develop disease [especially chorioretinitis] later in life if they are not diagnosed and treated.)

**Toxoplasmosis in animals**

In cats

* In addition to serving as a source of infection for human beings, cats can also develop clinical toxoplasmosis themselves. Infection can affect virtually any organ in the body, so clinical signs are varied. Among the more common presentations are:
  - **fever of unknown origin**
  - uveitis/chorioretinitis (keratic precipitates, aqueous flare, retinal detachment) and associated intraocular disease (Ocular disease can present in the absence of other systemic signs of infection.)
  - encephalitis
  - polymyositis
  - pneumonitis
  - hepatitis
  - “fading kitten syndrome” following transplacental infection -- In one experimental study (Dubey, Lappin and Thulliez, 1995), most kittens born to queens infected during pregnancy died within 24 hours of birth. Kittens that survive may shed oocysts.
In dogs
* Clinical disease is rare, but can be manifest as:
  - severe, rapidly fatal systemic disease involving the respiratory and GI tracts and the liver
  - meningomyeloencephalitis and/or polymyositis
    -- Ocular disease occurs much less commonly in dogs than in cats.

In other domestic animals
* The most important manifestation of *Toxoplasma gondii* infection in farm animals is abortion in sheep and goats (very rarely cattle). For instance, sheep farmers in the Midlands of Tasmania in Australia are estimated to have lost 15-50% of their lambs to *Toxoplasma* abortions and stillbirths in 2003-2005.
  - Infection in non-pregnant ruminants and horses is generally asymptomatic, but uveitis/chorioretinitis can occur.

In marine mammals
* Toxoplasmosis has been suggested as one cause for an increase in marine mammal mortality throughout many areas of the world (in particular sea otter mortality along the western continental US and Alaskan coast). CNS effects of infection may make the otters less able to avoid predation by sharks. The source of infection has been suggested to be run-off containing cat waste, but there was no correlation between sewage exposure and infection in the otters in 2003. However, *T. gondii* oocysts can sporulate and survive for months in seawater, and anchovies, a common prey fish, have been suggested to be able to filter and concentrate *T. gondii* oocysts. Severe disease in marine mammals has also been suggested to be associated with dual parasitism with *T. gondii* and *Sarcocystis neurona*.

Diagnosis of *Toxoplasma gondii* infection in cats and dogs
* CBC/serum chemistry/radiographic findings vary depending on the organ(s) involved.
* Tachyzoites are rarely found in CSF fluids or FNAs of tissues. However, they may be identifiable in thoracic or peritoneal effusion fluids.
* PCR assays for use on serum, aqueous humor or CSF; ELISA for detection of *Toxoplasma* antigens (Caution: it is possible to detect *T. gondii* by PCR in the aqueous humor without active disease.)
* Clinically affected cats are rarely shedding the organism, so fecal analysis for the presence of organisms is not useful. When present, oocysts of *Toxoplasma* are much smaller than *Isospora* organisms. But remember, cats only shed oocysts for 10-14 days immediately after infection, which is prior to the onset of clinical signs.
* Serologic diagnosis:
  - To serologically support a diagnosis of toxoplasmosis, one should have either a (+) IgM titer or a 4-fold increase (or decrease) in IgG titer, along with compatible clinical signs.
    -- IgM ELISA titers rise within 2-4 weeks of infection; titers typically revert to (-) by 12 weeks, but can occasionally persist for many months.
    -- IgG ELISA titers rise within 3 weeks of infection; titers persist for years.
    -- Maternal antibodies in kittens disappear by 12 weeks of age.
    -- One can look for evidence of active antibody production in the local aqueous humor or CSF compartments via calculation of an “antibody coefficient”:
      \[
      \text{Ab coef} = \frac{\text{Toxoplasma titer in local compartment}}{\text{Serum titer to unrelated Ag}} \times \frac{\text{Toxoplasma titer in serum}}{\text{Local compartment titer to unrelated Ag}}
      \]
      --- Coefficients >1 (ideally >8) are suggestive of active Ab production in the local compartment.
Treatment of *Toxoplasma gondii* infection in cats and dogs

*Clindamycin* is currently the drug of choice in both dogs and cats (although there are reports of deaths in experimentally infected cats treated with clindamycin [Plumb, 1995]).

- dogs: 5-20 mg/kg BID; cats: 12.5-25 mg/kg BID
  -- Side effects include anorexia, vomiting and diarrhea.

*Previously, combination therapy with pyrimethamine and sulfonamides was used, but this required folic acid supplement to alleviate side effects.*

Mechanisms to reduce human infection with *Toxoplasma gondii*

* properly cook meat and wash hands and utensils following contact with raw meat
* wear gloves when gardening or otherwise coming into contact with soil
* thoroughly wash fresh vegetables
* remove feces from litter boxes daily (since sporulation to an infectious form requires several days) and clean the boxes regularly (Boiling water is the only proven disinfectant other than treatment with 10% ammonia for 10 minutes, which is potentially very irritating for the person performing the cleaning.)
* avoid litter boxes and gardening immediately prior to and during pregnancy
* don’t feed cats raw meat
* maintain cats as totally indoor pets to avoid hunting and infection from rodents
* keep cats out of pig, sheep and goat barns

Vaccination of cats to reduce their role as reservoirs of the organism?

*Goal: prevention of oocyst shedding by cats* (not necessarily complete protection from infection)

- An early approach was to intentionally infect cats and then treat with monensin or pyrimethamine/sulfadiazine to prevent shedding from this “immunizing infection.” When these cats were re-challenged, 85% failed to shed the organism - effective, but risky!
- T263 vaccine strain of *T. gondii*: a mutant strain that infects cats and undergoes partial enteroepithelial replication, but does not complete sexual replication to produce oocysts.
  -- Up to 100% protection from shedding upon subsequent challenge has been achieved following T263 infection/vaccination. But there are still questions about the safety of its use in cats with prolonged (>11 months) FeLV infection.

References


Cat Scratch Disease and other *Bartonella*-related Diseases

*Bartonella henselae*

Cat scratch disease (CSD) has been recognized as a clinical entity in humans since the early 1900's, but the specific etiological agent alluded investigators until recently. Initially, herpesviruses, *Chlamydia* and *Pasteurella* had been suggested as causes. Then in the 1980's, a curved rod was identified in tissues of CSD lesions by silver staining. This was the first real hint to the etiology of CSD. Initial identification of the silver-staining agent as *Afipia felis* did not hold up in additional cases, either by bacterial culture or serologically. In 1992, *Bartonella henselae* was isolated from and identified by PCR in CSD lesions. Previously classified as *Rochalimaea henselae*, these are slightly curved, Gram (-) rods, consistent with the original silver-staining results.

- The *Bartonella*, *Rochalimaea* and *Afipia* genera are all related phylogenetically to the *Rickettsia* and *Ehrlichia*.

With this etiologic understanding, we can now link CSD to other diseases of humans caused by related *Bartonella spp.*, and we can better understand the epidemiological role of cats and other animals in these diseases.

**CSD in humans:**

* There are about 22,000 cases of CSD in the U.S. each year.
* Cat scratch disease is manifest most commonly as a series of **papules and pustules around a cat scratch** (59-93% of patients). These typically develop within a few days of the scratch and the **scratch itself may persist as a non-healing wound**. This stage of disease is followed 7-50 days later by the development of a **regional lymphadenopathy** (>90% of patients) in nodes proximal to the scratch, most commonly the lymph nodes of the axilla, neck or groin and sometimes affecting multiple nodes. (The nodes only rarely suppurate.)
  - Patients may also have fever (32-60% of patients), headache and malaise (13-29% of patients), but most patients generally feel well.
  - Histologically, affected nodes are characterized by necrotizing, granulomatous inflammation and **micro-abscess formation**.
    -- Patients historically underwent surgical biopsy and histopathologic analysis of the enlarged lymph node to rule out lymphoid neoplasia. Although this practice has decreased in recent years, there may be reason to return to more frequent use of biopsy for histopathology and culture, as a recent study found that 26% of CSD-suspect lymph nodes biopsied had evidence of neoplasia.
  - Patients with bartonellosis (with or without initially diagnosed CSD lesions) occasionally develop more chronic lesions in other locations that pose more serious health concerns, both among immunocompromised hosts and immunocompetent patients (see below). These systemic infections are consistent with the recent finding that an untreated CSD lesion served to seed the bloodstream of a patient with *B. henselae* for several months following initial localized infection, and with the detection (using combined enrichment culture and PCR) of *B. henselae* or *B. vinsonii subsp. berkhoffii* among individuals with animal contact and chronic or intermittent non-specific symptoms.
* **Bartonella** infections in humans are diagnosed serologically (IFA, ELISA assays), based upon either a single high IgG titer or a 4-fold rise in IgG titers or a positive IgM titer, or by culture or PCR detection of the organism.
* There are two different genotypes of *B. henselae* now recognized. Both can cause CSD, but there is some data to suggest that genotype II strains may be more pathogenic for humans than type I strains.
* The value of antibiotics in the treatment of uncomplicated CSD in people is unclear. Most health care providers feel that antibiotics do not significantly alter the course of disease (lymphadenopathy typically regresses in 2-6 months without treatment), although azithromycin, which penetrates lymph node tissue and concentrates intracellularly, may be effective in reducing the size of the affected node(s). Data published in 2010 suggested that enrofloxacin and pradofloxacin were more efficacious against *B. henselae* in *in vitro* susceptibility assays. Doxycycline or erythromycin therapy for 8-12 weeks is used in more severe infections in immunocompromised persons - see below.

**CSD in children:**
- The *prevalence of CSD is highest in children*. Approximately 57-80% of CSD cases occur in children and young adults <21 years of age (highest age-specific incidence is in children <10 years of age).
- **Children with CSD are also more likely than healthy adults to develop complications of *B. henselae* infection beyond simple CSD:**
  -- **persistent fevers, fevers-of-unknown-origin (FUO), and/or systemic spread of the organism (e.g., to abdominal lymph nodes, liver, spleen, bone)**
    --- ~5% of cases of FUO are attributed to *B. henselae* infection (Jacobs and Schutze, 1998).
  -- **“Parinaud’s oculoglandular syndrome”** (ocular granuloma or conjunctivitis and preauricular LN’opathy; following inoculation of *B. henselae* into the conjunctiva)
  -- **encephalitis** 1-6 weeks after the onset of LN’opathy

**Non-CSD Bartonella infections in immunocompromised patients (less commonly in immunocompetent people):**
* WITH THE ONSET OF AIDS, *B. HENSELAE* HAS TAKEN ON MUCH GREATER SIGNIFICANCE AS A PATHOGEN OF HUMANS. *Bartonella henselae* infection is now known to cause, in addition to CSD:
  - **“bacillary angiomatosis”** - a lobular proliferation of blood vessels and inflammatory cell infiltrates in the skin (may resemble Kaposi sarcoma lesions)
    -- *B. henselae* can induce the production of vascular endothelial growth factor and stimulate angiogenesis both *in vivo* and in an *in vitro* endothelial cells model.
  - **“peliosis hepatis”** - a disease in which blood-filled cystic lesions develop in the liver (and sometimes the spleen), associated with hepatosplenomegaly, abdominal pain and nausea
  - granulomatous, necrotizing hepatitis and splenitis, even progressing to spontaneous splenic rupture and hemoperitoneum
  - **endocarditis** (esp. in patients with underlying valve disease or prosthetic valvular devices)
  - osteomyelitis
  - uveitis (especially in patients of HLA-B27 type), neuroretinitis, anterior uveitis, vitritis, choroiditis, retinal vascular occlusions, retinal detachment, orbital abscess
  - prolonged bacteremia and **persistent fevers**
  - breast abscesses (in one case associated with contact with a guinea pig rather than a cat)
  - a variety of neurologic manifestations, including cerebral arteritis and stroke, myelitis, encephalitis, seizures, coma and neurocognitive decline. (A study in 2008 by Breitschwerdt *et al.* documented headaches and/or neurologic disease +/- cognitive dysfunction in patients with defined cat or biting insect contacts.)
    -- There has been some suggestion that neuropsychological decline (“AIDS dementia”) in AIDS patients may be related to *B. henselae* infection, though data in this regard is inconclusive.
The role of cats as risk factors for CSD in humans:
* *Bartonella* is now widely considered the most common zoonosis associated with cats. Seroprevalence- and culture-based studies indicate that infection with *Bartonella* bacteria is quite common in cats in many parts of the world. By way of example, a study published in 2004 of pet cats (3-24 months of age) in the U.S. found that 24% were bacteremic and 51% were seropositive for exposure. Other estimates are that 55-81% of cats in the U.S. are seropositive for exposure. In addition, cats maintain a prolonged bacteremia (up to 22 months) with *B. henselae*.
* Cats are clearly the most important epidemiological risk factor for infection of humans:
  - Greater than 90% of CSD patients have had some form of contact with cats, 75% of CSD patients have a documented scratch or bite, and there are clear epidemiological links between CSD and owning a sero (+) or a bacteremic cat.
  - Kittens are a greater risk than adult cats. (Infection is more common in cats < 2 years of age and kittens are also more playful and more likely to cause scratches.)

CSD as an occupational hazard for veterinarians?
* As you might expect, a survey conducted at a veterinary medical conference in Ohio suggested that the rate of *B. henselae* seropositivity in veterinarians (6%) is higher than that in the general public.

Ectoparasites as vectors?
Fleas:
- There is PCR evidence of *Bartonella* DNA in fleas, *Bartonella henselae* can be cultured from fleas, and fleas have been shown experimentally to transmit the organism from cat-to-cat. In fact, direct cat-to-cat transmission from bacteremic to in-contact naive cats in the absence of fleas has not been demonstrated, further supporting the role of fleas as vectors.
- Flea infestation was a specific risk factor for infection among cats in the U.S. in a study published in 2006, as was age <6 months and adoption from a shelter or as a stray cat.

Ticks:
- DNA of several *Bartonella* spp. has been detected in *Ixodes pacificus* ticks in California and in *Ixodes ricinus* ticks removed from human beings in Italy, *B. henselae* has been isolated from tick bite skin lesions in people, and tick infestation may be a risk factor for *Bartonella* infection in dogs. (see below)

Flies:
- *Bartonella* DNA has been detected in horn flies and a stable fly.
* However, it is not yet known whether these vectors can actually transmit *Bartonella* to humans.

Infection and disease in cats?
* *Bartonella henselae* infection in cats has traditionally been considered to be subclinical (Regnery et al., 1996, Abbott et al., 1997). However, other studies have documented fever and additional clinical signs and/or lesions in cats:
  - Kordick and Breitschwerdt (1997) demonstrated transient anemia, CNS signs (behavioral changes) and LN’opathy after parenteral infection.
  - Guptill *et al.* (1997) demonstrated histologic evidence of microabscessation in the spleen and LN’opathy/LN granulomas following IV inoculation.
  - Kordick *et al.* (1999) demonstrated lymphocytic inflammation in a variety of organs, though minimal clinical signs.
  - Greene *et al.* (1996) demonstrated raised injection-site skin lesions and LN’opathy following “scratch” intradermal inoculation.
  - O’Reilly *et al.* (1999) and Mikolajczyk and O’Reilly (2000) experimentally induced disease in cats that was very similar to classical CSD in people, following intradermal inoculation with a specific strain of *B. henselae*. The cats developed raised, erythematous lesions at the
site of inoculation, along with fever, lethargy and in some cases palpable LN’opathy.
- Lappin and Black (1999) suggested that uveitis in a cat was associated with *Bartonella* infection. The cat was sero (+) for *Bartonella spp.*, had *Bartonella* antibodies in its aqueous humor, and responded to doxycycline.
- Chomel *et al.* (2003) documented fatal endocarditis in a cat with *B. henselae* infection.

**Diagnosis of *B. henselae* infection in cats:**
* serologic testing (IFA; combined ELISA/immunoblot - In the later case, ELISA is used for initial screening and immunoblot is used to distinguish true from false positives.)
* blood culture
* PCR
- Importantly, a (-) serologic test in a cat is highly predictive of that cat NOT being bacteremic. Therefore, it may be wise to recommend that immunocompromised patients only acquire sero (-) adult cats. Conversely, cats may remain seropositive beyond the time of active bacteremia.

**Treatment of cats to eliminate the organism?**
* In one report, antibiotics (erythromycin or tetracycline) reduced the level of bacteremia following experimental infection of cats, but the duration of bacteremia was not affected (Regnery *et al.*, 1996).
In a second report (Greene *et al.*, 1996), doxycycline, amoxicillin, enrofloxacin and amoxicillin/clavulanate were all variably effective in reducing the duration of bacteremia compared to historical data from untreated cats, but there were no concurrent untreated controls in this study, so???
- Overall, antibiotic therapy is unlikely to immediately eliminate the organism and the risk of transmission to humans. It will be interesting, however, to determine whether azithromycin will be a useful drug to terminate bacteremia in cats in addition to reducing the symptoms of CSD in people.

**Vaccination of cats?**
* Incorporation of a *B. henselae* vaccine into the routine kittenhood vaccination regime may be a useful mechanism to reduce the role of cats as a reservoir of infection, and thereby, to protect people in contact with cats.
* Results of several studies indicate that cats which naturally eliminate the infection are resistant to subsequent re-challenge (Greene *et al.*, 1996; Regnery *et al.*, 1996; Abbot *et al.*, 1997), so vaccination may be an option. However, it’s unclear what immunologic factors are responsible for immunity in cats. Since cats maintain prolonged bacteremia in the face of strong antibody responses, it is unlikely that antibodies alone can clear the organism.
- Protection from the effects of antibodies and other immune responses may be related to the fact that *Bartonella* organisms can infect and persist inside erythrocytes.

**Other hosts/other *Bartonella spp.*:**

**B. henselae infection in dogs?**
* There are several reports suggesting that CSD in people can be associated with contact with dogs rather than cats harboring *B. henselae*. The overall role of dogs in the epidemiology of CSD is not well established, and is likely to be far less important than that of cats. However, *Bartonella* DNA has been identified in dog saliva.
- *Bartonella henselae* infection is also a health concern for dogs themselves, as evidenced by the fact that peliosis hepatis and associated serosanguinous peritoneal effusion have been observed with *B. henselae* infection in a Golden Retriever, and both *B. henselae* and *B. clarridgeiae* (see below) have been isolated from dogs with granulomatous hepatitis.
Seropositivity alone to *B. henselae* does not appear to be statistically associated with disease more generally, but *Bartonella spp.* were detected in 19% of cases of blood culture-negative endocarditis in dogs in a 13-year case review at UC-Davis. These dogs were often afebrile and had shorter survival times compared to other cases.

- Serosurveys in the U.K., Hawaii, and Japan have demonstrated *B. henselae* seroprevalence rates in dogs of 3-7.7%.

**B. clarridgeiae, B. koehlerae and B. quintana infections (cats, dogs):**

* Bartonella clarridgeiae* has been isolated from persistently infected cats, and, in 1997, CSD in a veterinarian was associated with *B. clarridgeiae* rather than *B. henselae* infection. The organism was also cultured from a 6-week-old cat the veterinarian had adopted. Co-infection of cats with *B. clarridgeiae* and *B. henselae* has been demonstrated serologically in France.

- The involvement of *B. clarridgeiae* or antigenic variants of *B. henselae* in CSD may explain why a portion of human CSD patients can remain seronegative to *B. henselae*.

* Bartonella clarridgeiae* has been isolated from dogs with valvular endocarditis and granulomatous hepatitis.

* Bartonella koehlerae* has been isolated from human cases of endocarditis and cats.

* Bartonella quintana* causes “trench fever” and endocarditis in persons typically living in under poor hygienic conditions (times of war, homelessness) and is most commonly transmitted by the human body louse, *Pediculus human corporis*. However, cases have also rarely occurred in people living under highly hygienic conditions, but in close contact with cats, and the organism has also been isolated from cats and dogs, including a dog with endocarditis.

**Bartonella vinsonii infections (dogs, coyotes, gray foxes):**

* Bartonella vinsonii subsp. berkhoffii* was initially identified as a cause of vegetative valvular endocarditis in dogs in N. Carolina and Virginia, and a serosurvey found a 3.6% seropositivity rate among dogs in that area. Risk factors for seropositivity in that study included living in a rural environment, running free and a history of heavy tick infestations. Many of the dogs were also sero (+) for *Ehrlichia canis*, further supporting the possibility of tick transmission of *B. vinsonii*.

* B. vinsonii subsp. berkhoffii* has been further associated with myocarditis, endocarditis, cardiac arrhythmias and granulomatous lymphadenitis and rhinitis (and sometimes epistaxis) in additional dogs. Chronic infection may be associated with impaired immune responses in dogs.

- A study has demonstrated antibodies to *B. vinsonii* subsp. *berkhoffii* in 8.7% of 1,872 U.S. Government working dogs, with a significantly higher risk for seropositivity among dogs in the southern U.S.

* In coyotes, seropositivity against *B. vinsonii* was identified in 7-51% of animals tested in California, and 28% of coyotes tested in California were specifically found to be bacteremic.

- **Human infections** with *B. vinsonii subsp. berkhoffii* have been documented in a child who was bitten by a coyote in California, a man in London with endocarditis, and a child (epithelioid hemangioendothelioma) and a dog (hemagiopericytoma) with vasculoproliferative lesions.

* In gray foxes in California, *B. vinsonii subsp. berkhoffii* or *B. clarridgeiae*-like organisms were isolated from 9.4% and 42%, respectively, of foxes tested in 2003-2004.

**Bartonella elizabethae and dogs:**

* Bartonella elizabethae* is a cause of endocarditis and retinitis in human beings and has been isolated from dogs with non-specific signs of illness.

**Ruminants and Bartonella infections:**

* Bartonella spp. (e.g., *B. bovis, B. capreoli, B. chomelii, B. schoenbuchensis*) have been isolated
from domestic cattle as well as mule deer and elk in the western U.S., from roe deer in France, and from sheep blood. Whether these ruminant agents pose a human health risk or impact the health of the animals remains unclear. However, *B. bovis* has been isolated from vegetative endocarditis valvular tissue samples from cattle, and one survey found that 59% of 448 cattle in a herd in France were bacteremic at a single sampling time point. Bacteremia in this herd was most common in the last 2/3rd of pregnancy; no negative impacts on reproductive parameters or milk yields.

**Rodents and Bartonella infections:**
* A number of different *Bartonella* species associated with human disease have been isolated from various species of rodents:
  - An isolate from ground squirrels called *B. washoensis* has also been recovered from a human patient with myocarditis and a dog with mitral valve endocarditis.
  - Another typically rodent-associated species called *B. elizabethae* has been isolated from or identified in tissues from both a human patient and a dog.
  - Neurologic and cardiac disease have been documented in association with *B. vinsonii* (subsp. *arupensis*) infections.
    -- In a 2009 study in Japan, 142 of 546 imported exotic small mammals were carrying *Bartonella* spp., including human pathogenic strains. Animals that had been wild caught were significantly more likely to be infected compared to facility-bred animals.

**Other examples:**
* *B. alsatica* has been isolated from healthy wild rabbits in France and from human beings presenting with endocarditis or lymphadenitis who had fed and/or butchered rabbits in France.
* *B. henselae*, *B. koehlerae* and *B. vinsonii* subsp. *berkhoffii* DNA has been amplified from feral pig blood samples in North Carolina.
* *Bartonella* spp. have been isolated from raccoons in CA.
* *B. henselae* DNA has been amplified from the blood of free-ranging porpoises, kangaroos, and loggerhead sea turtles.
* *Bartonella* of 21 different genetic variants were cultured from bats in Guatemala and *Bartonella* have also been identified in bats in Kenya.

**References**


Saunders Elsevier; Maryland Heights, MO.


Animal Bites

* Americans own large numbers of pet animals. According to 2007 data from the AVMA:
  - 37.2% of U.S. households owned a dog.
  - 32.4% of U.S. households owned a cat.
  - It is estimated that there are ~72.1 million dogs and ~81.7 million cats kept as pets in the U.S.

* Given these large numbers of pets, it is perhaps not surprising that animal bites are numerically the most common zoonosis!
Some U.S. animal bite statistics to consider:
~4.5 million animal bites occur each year (CDC data)
- 1 out of every 2 people will be bitten by a dog or cat during their lifetime.
  -- Up to 92% of veterinarians report being bitten over their lifetime.
- Bites result in ~334-368,000 ER visits/year, representing approximately ~0.2-1.5% of all ER visits, at an annual cost of ~$165 million in direct health care expenses and a total cost of ~$250 million. More cat bites require medical attention and are associated with higher rates of infection than dog bites.
- Approximately 1-4% of bites require hospitalization.
- The majority of bites (80%) are from dogs.
- Approximately 30-85% of bites are due to the family’s own dog or a neighbor’s dog.
- Children are the most frequent victims of dog bites, with 5-9 year-old boys having the highest incidence.
- Men are more frequently bitten by dogs than are woman (3:1), whereas woman are more frequently bitten by cats (3:1).
- From 1979-1996, dog bites resulted in >300 deaths in the U.S. There is little evidence for specific breed predilections in the overall prevalence of bite incidents. However, pit bull-type dogs and Rottweilers are responsible for >50% of FATAL attacks.
  -- 80% of deaths in 1995-1996 were among kids <11 years of age.

Bites can result in:
* pain
* disfigurement and loss of function (A small percentage of bites result in permanent disability, especially bites to the hands.)
* exsanguination and death (especially with large dog bites to the face or neck of children)
* INFECTION
  - transmission of specific zoonotic infectious agents such as Bartonella henselae, Yersinia pestis, Francisella tularensis, rabies virus
  - wound infections (occur in ~5-15% of dog bites, but up to 80% of cat bites):
    -- local cellulitis/abscessation
    -- osteomyelitis (This is particularly a problem with bites to the hands and feet because of the proximity of the underlying bones to the skin surface. These wounds must be treated aggressively.)
    -- bacteremia and seeding of internal organs (CNS, heart, kidneys, lungs)
    -- DIC, endotoxic shock, death

Organisms of most concern:
- PASTEURELLA MULTOCIDA and Pasteurella spp.
  -- Pasteurella bacteria are common oral flora organisms in dogs and cats (50-66% of dogs; 70-90% of cats) and are implicated as a major pathogen in 20-50% of infected dog bites and an even higher % of cat bites.
  -- Infections rapidly lead to cellulitis, with subsequent abscessation, osteomyelitis, septic arthritis and potentially systemic dissemination (esp. to the lungs).
- “CDC alphanumerics” (slender, Gram [-] rods)
  -- Capnocytophaga canimorsus (CDC DF-2) (“dysgonic fermenter-2”)
    --- In one study, 73% of 53 dogs presented to a veterinary medical clinic were colonized in their mouths with this organism.
    --- This is a particular concern for splenectomized (and other immunosuppressed) patients, with a 30% case fatality rate with C. canimorsus septicemia.
Recently, *Capnocytophaga* was implicated as the cause of chronic sinusitis and rhinitis in a cat. Previously, the potential for this bacterium to cause disease in animals themselves has not been appreciated, perhaps because of its fastidious *in vitro* growth requirements.

--- CDC NO-1 (“non-oxidizer”; similar in characteristics to *Acinetobacter*)
--- another recently described alphanumeric organism associated with dog bites (77% of isolates) and, to a lesser degree (18% of isolates) cat bites
--- wound infections capable of producing septicemia - 58% of 22 victims in one study required hospitalization.

--- CDC IIj (*Bergeyella* spp.)
--- present in the oronasal fluids of up to 90% of dogs, but its importance as a human pathogen is unclear since its fastidious growth means that it is rarely isolated from bite wounds
- *Staphylococcus* and *Streptococcus*
- *Proteus, Klebsiella, Enterobacter*
- *Bacteroides, Clostridium* (require anaerobic culture to identify!)
  -- *Erysipelothrix rhusiopathiae* (normally associated with pigs) has been isolated from cat bites.
- *Dog and cat bite wounds are often colonized by a mixed flora of both aerobes and anaerobes!*

**Bites from other animals:**
* *Serratia marcescens* infection has been associated with an iguana bite.
* Bites (or scratches) from rats (and less commonly other species, including other rodents, dogs, cats…and in one case, a rooster!) can lead to “rat bite fever,” a syndrome of fever, rash, myalgia and arthralgia, vomiting, rash, and lymphadenitis, that occur days to weeks following infection with *Streptobacillus moniliformis* (U.S.) and *Spirillium minus* (Asia). Disease carries a 7-10% case fatality rate if untreated. Additionally, *S. moniliformis* can also be acquired by ingestion as a foodborne disease, leading to the “Haverhill fever” form of infection accompanied by muscle and joint pain.
* *Halomonas vensuta* (a halophilic, Gram [-] rod) infection has been associated with a salt water fish bite, *Vibrio* spp. infections are most commonly associated with salt water environments, and MRSA infections have also been associated with ocean water.
* *Aeromonas* spp.-induced cellulitis, septicemia, and diarrhea are most often associated with freshwater environments, as are aquatic species of *Edwardsiella.*

**References**


Streptococcus Infections as Zoonoses

The streptococci are a large family of Gram (+) bacteria. The streptococci are classified by the degree of hemolysis they cause on blood agar and by the so-called “Lancefield” classification scheme that is based on antigenic differences in their cell wall carbohydrates. The Lancefield groups most commonly causing disease in humans are Groups A, B and C (less commonly D, G, L, M):

**Group A**

* S. pyogenes - pharyngitis, rheumatic fever, streptococcal toxic shock syndrome, necrotizing fasciitis in humans

* Recurrent Group A Streptococcus (GAS) infections (“strept throat” and otitis media) are a common problem in many families with young children. A QUESTION OFTEN ARISES AS TO WHETHER DOGS OR CATS IN A HOUSEHOLD CAN SERVE AS SOURCES OF INFECTION FOR HUMANS WITH GROUP A STREPTOCOCCUS? - This point is still debated in the literature. Clearly, human beings are the primary reservoir for GAS, not dogs and cats, so when animals in a household are infected, this is an example of a reverse zoonosis (animals are colonized subsequent to spread from a human being). The question is, can dogs or cats then subsequently pass the infection on to other people? Some studies (Crowder et al., 1978; Wilson et al., 1995) have found no correlation between the presence of dogs in a household and human GAS infections, while others (Mayer and VanOre, 1983; Copperman, 1982) have documented resolution of chronic GAS in households after isolation of the organism from, and treatment of, dogs.

-- I have personally been involved in two clinical situations in which Group A S. pyogenes was cultured from both the household dog and children suffering from recurrent pharyngitis. In both of these cases, all of the people in the house had previously been treated simultaneously without eliminating the problem. However, when all the people in the household and the dog were simultaneously treated with antibiotics, the problem resolved.

- To my knowledge, there is only one case report suggesting involvement of cats. (Roos et al., 1988)

**Diagnosis of GAS infection in dogs:**

- It is important to realize that the dogs are asymptomatic for GAS infection.
- It has historically been suggested that cultures for GAS in dogs should be taken from the caudal wall of the pharynx, ideally the tonsils/tonsillar crypts. This generally requires sedation so as to avoid contamination of the swab with extraneous oral surface commensals that will outgrow and mask GAS.
  -- It has also been suggested that the optimum sample site for detection of GAS in dogs is the conjunctival sac.
- It is critically important in household outbreak situations to have the human and canine isolates typed to be sure that both are identical, above and beyond simply both being beta-hemolytic.
  -- To accomplish this, it is important that veterinarians and physicians communicate and work closely together.

**Treatment:**
- The antibiotic of choice for *S. pyogenes* remains penicillin.

**Group G**
* The most important *Streptococcus* from dogs and cats is Group G *S. canis*. This organism causes otitis media, neonatal septicemia, cervical lymphadenopathy, polyarthritis, and reproductive tract infections with abortion and mastitis in dogs. It also causes neonatal sepsis in cats.
* *Streptococcus canis* has also been recovered from dog-owning human beings with chronic ulcerative skin lesions and/or cellulitis and/or bacteremia. Such infections may be more frequent than reported because of misidentification of *S. canis* as group C *Streptococcus*.
  - Beyond the potential for zoonotic infections from domestic dogs and cats, Group G infections in people have also been linked to direct contact with jerboas.

**References**

**Bordetella bronchiseptica as a Zoonosis**

* Gram (-), small bipolar rods

*Bordetella bronchiseptica* infections in animals:
* tracheobronchitis (“kennel cough”) in dogs
* upper respiratory infection and tracheobronchitis in cats
  - Studies also indicate that approx. 3% of shelter cats may be subclinically shedding *Bordetella bronchiseptica*.
* “snuffles” in rabbits (also Pasturella)

*Bordetella bronchiseptica* infections in humans:
* This is an uncommon infection in humans that generally produces a relatively non-threatening, “whooping cough” (normally caused by *Bordetella pertussis*)-like syndrome in immunocompetent individuals. However, *B. bronchiseptica* has also been associated with endocarditis, peritonitis, meningitis, and wound infections. In some cases, a direct connection to animals is obvious, e.g.,
  - a 79 year-old woman with pneumonia [4 times!] who had regular contact with rabbits on her farm - The human and rabbit isolates were identical!
* *Bordetella bronchiseptica* is being isolated increasingly from immunocompromised people or people with underlying pulmonary pathology (e.g., cystic fibrosis). In these patients, respiratory tract infections range from sinusitis to pneumonia/pleuritis.
* *Bordetella avium* has also on rare occasions been isolated from humans with respiratory disease.

((*Pasteurella dagmatis* and *Neisseria canis*, Gram-negative potential members of canine oral flora, have also been isolated from a patient with chronic bronchial disease - she owned a poodle.))

**References**
**MRSA/MRSI as Zoonotic Infections**

**Methicillin-resistant *Staphylococcus aureus* (MRSA)**

* Reverse zoonotic infections of animals (most commonly dogs, cats, horses, pigs and cows) with human-origin *Staphylococcus aureus*, including dangerous methicillin-resistant (MRSA) strains, have been documented for several years (specific routes of transmission not thoroughly understood). This phenomenon has paralleled the emergence of MRSA as a community-acquired pathogen among human beings.

* Importantly, there is now strong evidence that MRSA strains, once introduced into a population of animals (horses, pigs, dogs, poultry), may be maintained through animal-to-animal transmission (including subclinical infections), with the potential for subsequent transmission back to people. For example, a specific strain of MRSA has emerged since 2003 in Europe, initially in The Netherlands and subsequently elsewhere on the European continent and the UK, among people associated with pigs (and cattle), with spread to become responsible for >20% of all MRSA isolates within the human population in The Netherlands. This same strain has also been isolated from swine and swine workers in Canada and the U.S. Among pets, there are clear examples of humans and dogs or cats in a household simultaneously infected with indistinguishable strains of MRSA.
- For an excellent summary of MRSA, see the AVMA backgrounder article at: http://www.avma.org/reference/backgrounders/mrsa_bnd.asp

* Among exotic species, MRSA has also been isolated from free-ranging and captive marine mammals, and from an elephant calf and its zoo caretakers.

**Staphylococcus intermedius group organisms**

* The coagulase-positive *Staphylococcus* spp. most commonly isolated from animals (*Staphylococcus intermedius, pseudintermedius* and *delphini*, now grouped together as “*Staphylococcus intermedius* group”) can result in zoonotic infections, especially following dog bite wounds, but also rarely in cases of systemic human infection without an obvious animal contact.

* Methicillin resistance also occurs among *Staphylococcus intermedius* group organisms (MRSI). MRSI strains have been isolated from both animal and human infections.

**References**


Selected Zoonotic Bacterial Agents of Gastroenteritis That Can Be Acquired from Dogs and Cats

Gastroenteritis is a very common problem in both dogs and cats, particularly among puppies and kittens, and the list of possible infectious etiologies is extremely long. Of interest here is the fact that many of these agents are also of concern as human pathogens, in particular for immunocompromised individuals. Although these organisms are most commonly acquired as water- and foodborne infections, dogs and cats (and other domestic animals) may pose a direct zoonotic risk. For example, a study of cats in Colorado in 2000 (Hill et al.) demonstrated that 13.1% of cats were shedding zoonotic agents of gastroenteritis in their feces, including 5.4% shedding Cryptosporidium parvum, 2.4% shedding Giardia intestinalis and 2.0% shedding either Salmonella typhimurium or Campylobacter jejuni. Additionally, feeding raw meats to dogs and cats poses risks for their infection with many agents of gastroenteritis, and subsequent transmission of these agents to people.

**Campylobacter jejuni**

* Gram (-), curved, “gull wing” rods with “chaining” of organisms end-to-end may mimic spiral spirochetes
**Poultry, ruminants and swine:** *Campylobacter jejuni* can be part of the normal flora of the GI tracts of these animals. Human infections can occur via direct contact with animal feces, consumption of contaminated raw milk (including raw milk labeled as “pet food” and raw milk converted into soft cheeses) or untreated/contaminated water (even just swimming in contaminated water or recreational sporting events – some strains may be better adapted than others to survival in the environment in surface waters), or most commonly, via consumption of **contaminated, undercooked meat**. In addition, flies have been shown to carry *Campylobacter* and have been implicated as a possible indirect source for human exposure to animal feces and *Campylobacter* infection. (In an unusual scenario in 2011, two farm hands in Wyoming were infected after having used their teeth to castrate young lambs…)

- **Poultry represent the most significant public health concern.** From 22-100% of commercial poultry products are contaminated, and this source accounts for 50-70% of all human cases. A study in the U.K. found that 100% of chickens raised organically outdoors carried *Campylobacter*, versus 58% of indoor conventionally raised birds. If the meat is thoroughly cooked, it poses no risk, but clearly this does not consistently happen even in restaurants, since consumption of restaurant-prepared chicken remains one of the most common sources of infection.
- A concern above and beyond the frequency of contamination is the occurrence of antibiotic-resistance among *Campylobacter* isolates from poultry. Studies have documented 14-84% resistance to antibiotics, including fluoroquinolones. Humans infected with ciprofloxacin-resistant strains suffer more prolonged diarrheal disease.

**Campylobacteriosis in humans:**

* Infection can involve the jejunum, ileum and colon, with edematous and hemorrhagic enteritis lesions. *Campylobacter jejuni* is the most common agent of bacterial diarrheal disease among humans in the U.S., with ~1-2 million cases each year. Clinical signs last for 1-7 days and include a prodrome of fever and malaise, followed by varying degrees of diarrhea and abdominal pain.
  - The incubation time is inversely related to the inoculum dose.
  - Anti-motility drugs for diarrhea increase the severity of symptoms and prolong the course of disease.
  - Disease is generally self-limiting, except in immunocompromised patients.

* In addition to GI disease, *C. jejuni* infection is considered the most common triggering factor for Guillain-Barre syndrome (GBS), an immune-mediated, primarily demyelinating myelitis/neuropathy. While ~70% of patients fully recover, the remainder suffer permanent sequelae, with ~8% unable to walk.
  - Evidence suggests that there is antigenic mimicry between the lipopolysaccharides of *C. jejuni* and GM1 or GQ1b gangliosides in human nervous tissue. However, other host factors may also be important in development of GBS (e.g., certain HLA genotypes).

**Some statistics:**

-- Approximately 1/1000 *Campylobacter* infections result in GBS.
-- ~40-66% of GBS cases follow *C. jejuni* infections.
-- GBS following *Campylobacter* is more severe, more likely to be irreversible.
- GBS may be associated with infection with certain serotypes of *C. jejuni* and strains with unique sequences in their fla A flagellar genes.

* Campylobacter infection is also associated with another immune-mediated disease in humans called “Reiter’s syndrome” [tenosynovitis with accompanying skin lesions, uveitis and urethritis]. This is estimated to occur in ~7% of patients with campylobacteriosis.
* Campylobacter infection has also been associated with development of myocarditis as a post-gastroenteritis sequelae, and fatal septic shock in a splenectomized patient, reflecting the potential severity of infection in immunocompromised individuals.
Campylobacteriosis in dogs and cats:
* Clinical signs of ileocolitis are most common in puppies and kittens <6 months of age. The chief presenting sign is diarrhea. (The diarrhea is thought to be due to the action of a cholera-like enterotoxin and a cytotoxin.) Severity varies from case to case, but exacerbated by stress.
  - Other signs such as vomiting, anorexia and fever are relatively uncommon.
  - The clinical course of disease is typically 1 week, but may be up to 3 weeks.
* Epidemiologically, living with dogs and cats is a specific risk factor for Campylobacter infection. Infections are most common in puppies and kittens, but Campylobacter spp. can also be isolated from clinically normal adult dogs and cats (at rates up to 30% in one study). One estimate is that ~5% of human infections are related to contact with dogs and cats. Finally, a report in 2004 documented concurrent infection of dogs and cats and human beings in a household with quinolone-resistant Campylobacter infections.

Diagnosis of Campylobacter infection:
* fecal culture (requires specific media and reduced oxygen culture conditions at 42C)

Treatment of Campylobacter infection:
* erythromycin (tylosin alternative) for 7 (up to 28) days is the drug of choice in dogs and cats
  - Renewed shedding after completion of the course of antibiotics is possible, so follow-up fecal cultures may be indicated.
    -- Azithromycin or erythromycin are most often used in human beings.

In addition to C. jejuni, humans can be infected with a variety of other species of Campylobacter that all are associated with animal reservoirs. These include:

- **C. upsaliensis** - diarrheal disease in dogs, cats and humans- **Dogs are a major reservoir in the world**, although there is some debate as to whether the same subtypes of C. upsaliensis are involved in causing disease in both dogs and humans.
- **C. coli**
- **C. hyointestinalis** - diarrheal disease in piglets, foals and humans; can be carried by dogs
- **C. fetus** - reproductive tract disease in ruminants; **systemic disease in humans**, especially immunocompromised (also human cases associated with reptile sources) – mode of transmission to humans is unknown

Salmonella enterica

* Our zoonosis discussion is focused on the many serotypes of Salmonella enterica.
  - Salmonella typhi and paratyphi (as well as Shigella) are typically only human pathogens and domestic animals play no role in the epidemiology of these infections. (Non-human primates may be infected and serve as a source for handlers, and S. paratyphi has been isolated from turtles as a source for human infection.) All of the other “non-typhoidal” Salmonella enterica serotypes are, however, ubiquitously present in the environment and reside in the GI tracts of many species of animals.

* The vast majority of human cases of non-typhoidal Salmonella infections are acquired not through contact with animals, but rather by ingestion of contaminated foods, e.g., Salmonella enteritidis from undercooked eggs and Salmonella typhimurium from undercooked meats or raw milk.
  - It has been estimated that shell-eggs still accounted for ~180,000 human infections in the U.S./year (2000). This includes organic shell eggs, e.g., outbreak in Minnesota in 2011.
One study of 200 meat samples from grocery stores in the Washington, D.C. area found that 20% contained Salmonella bacteria, and 84% of these Salmonella strains were resistant to at least one antibiotic. However, overall rates of Salmonella contamination of meats in the U.S. have been dropping in recent years, from 10.65% in 1998 to 1.6% in 2004 (USDA data). Nonetheless, meat-associated outbreaks continue, e.g., Salmonella Heidelberg associated with ground turkey in 2011, with at least 107 human cases over 31 states.

Beyond eggs and meat, Salmonella contamination of a variety of other foods has also been documented, e.g., Salmonella contaminated almonds led to a worldwide product recall in 2004, and contamination in 2006 forced a recall of 1 million chocolate bars.

Salmonellosis in humans:
* Salmonellosis is an extremely common disease among humans, with children and immunocompromised at higher risk. There are an estimated 1.4 million cases/year of non-typhoidal Salmonella infections, with 14,800-16,000 hospitalizations and 480-600 deaths. (More generally, CDC estimates that 48 million people suffer foodborne illness in the US annually, with 3000 deaths – Salmonella is the most frequent cause of hospitalization and death among these foodborne illnesses.)
  * Following a 6-72 (most commonly 12-36) hour incubation period, symptoms include fever, headache, diarrhea, abdominal pain, nausea, dehydration and possible septicemia/endotoxemia.
  * Serious complications of non-typhoidal Salmonella enteritis include a persistent bacteremia and fever syndrome, endocarditis or arteritis. Salmonella may also seed a wide variety of tissues and lead to local infections and/or abscessation of the hepatobiliary tree, spleen, urogenital tract, lungs, CNS, bones or joints.

Salmonellosis in dogs and cats:
* Disease severity varies:
  - subclinical carrier state (most common)
  - acute enterocolitis
    -- fever, anorexia, lethargy
    -- diarrhea, possibly with mucus or blood
    -- abdominal pain (Infection is often associated with mesenteric lymphadenitis.)
    -- septicemia/endotoxemia
    -- fetal death/spontaneous abortion/stillbirth
  - Cats may present with prolonged periods of fever and anorexia without diarrhea.
    -- “song bird fever” salmonellosis in cats - associated with predation on infected migratory birds

The role of dogs and cats in zoonotic transmission:
* Salmonella infections in dogs and cats deserve special comment for several reasons related to the potential for zoonotic transmission:
  1. Salmonella spp. can be isolated from healthy dogs and cats at rates up to 36% and 18%, respectively (up to 51% of shelter cats in a small-scale study in Belgium in 2003).
  2. Dogs and cats tend to shed Salmonella organisms for prolonged periods of time after infection.
  3. Dogs and especially cats can shed Salmonella organisms in both their feces and saliva, meaning that transmission can occur via licking.
  4. Pig ear and raw beef dog treats and raw meat diets may be a source of Salmonella infection for both dogs and humans who handle the foods. In addition, a multi-state outbreak of at least 79 human infections with S. schwarzengrand in 2006-2008 was linked to contact with dry dog food produced by a single manufacturer in Pennsylvania.
- In 2011-2012, the FDA is conducting a nationwide testing of pet food products for Salmonella because of concerns for human infection via either inadvertent handling exposure or purposeful ingestion.

5. **Salmonella typhimurium DT104** is a specific serotype of Salmonella typhimurium that has been associated with multidrug antibiotic resistance and serious disease in both animals and humans. It was first isolated in the United Kingdom in 1984 and was associated with human hospitalization rates approaching 50% and 5% mortality. The rate of isolation of DT104 skyrocketed in the United Kingdom, from 259 human cases in 1984 to 4,006 in 1996. Similarly, U.S. data from 1995, 1998 and 1999 showed that 28-31% of Salmonella typhimurium isolates had the R-type ACSSuT antibiotic resistance pattern of DT104.

- While infected cattle and their feces are clearly the most important risks for human exposure, it should be noted that multidrug-resistant Salmonella DT104 has also been isolated from 1-2% of cats in Scotland, and from pet birds. Furthermore, outbreaks of multidrug-resistant Salmonella infections have been documented among employees and clients of small animal practices and shelters in Idaho, Washington, Minnesota and New York since 1999 in association with infected cats and/or dogs.

6. **Dogs and cats may suffer salmonellosis as a “reverse zoonosis,”** with infection transmitted from human-to-dog and subsequently back to other humans. Similarly, outbreaks of Salmonella in large animal teaching hospitals have been linked to the introduction of bacteria from infected human personnel, with subsequent spread to animals and then back to other human workers. Bleach is the most effective disinfectant in veterinary hospital settings.

**The role of exotic pets:**
* Salmonellosis is well recognized as a zoonosis from reptiles, and all reptiles should be considered to be carriers of Salmonella. In the 1970s, it was estimated that 280,000 human cases of salmonellosis/year were associated with reptiles, leading to the ban in 1975 on turtles with carapace lengths < 4 inches (i.e., would fit in a child’s mouth). This led to an estimated reduction of 100,000 pediatric cases of salmonellosis each year, but a recent study has suggested that 6% of all sporadic human cases of Salmonella infection are still associated with reptiles (~74,000 cases/year). As specific examples, illegally sold small turtles led to infections in children in Wisconsin in 2004; multi-state outbreaks of human infections with Salmonella in 2007-2008 were linked to small turtle exposures. In 2002, there was even a report of a reptile owner who donated blood products and two transfusion recipients became infected with a strain of Salmonella matching that of the donor’s snake. (Specific information for distribution to clients on prevention of reptile-associated salmonellosis can be found at [www.arav.org/SalmonellaOwner.htm](http://www.arav.org/SalmonellaOwner.htm).)
* Amphibians are also implicated, e.g. 2009-2011 outbreak of human cases of S. typhimurium related to aquatic African dwarf frogs (224 human cases in 48 states).
* Salmonella infections (multidrug-resistant) were reported in 2003-2005 in over a dozen people from multiple states exposed to infected mice, rats or hamsters purchased through pet stores.
* Links are increasingly being recognized between specific animals and specific unusual serotypes of Salmonella, e.g.:
  - S. marina iguanas
  - S. java and S. poona turtles and lizards
  - S. tilene hedgehogs and sugar gliders
  - S. montevideo chickens/baby chicks (multiple outbreaks in the U.S. in 2006 and 2007; additional outbreak in 2011 of S. Altona associated with chick/duckling purchases from a nationwide feed store chain)
**Diagnosis of Salmonella infection:**
* fecal culture - best isolated using enrichment (e.g., tetrathionate and selenite F broths) and selective (e.g., MacConkey and SS [Salmonella-Shigella] agar) media

**Treatment of Salmonella infection??**
* Simple GI’itis should be treated with supportive therapy, fluids, etc. Treatment with antibiotics should be restricted to those patients that develop evidence of systemic spread of infection. (There is some debate as to whether antibiotics truly prolong shedding of Salmonella, as historically suggested. In either case, the use of antibiotics should still be restricted because of the ease with which Salmonella develop antibiotic resistance.) Animals: trimethoprim-sulfa, chloramphenicol, amoxicillin; humans: ciprofloxacin, azithromycin.

**Yersinia enterocolitica**
* Gram (-) rods

**Yersinia enterocolitica**
* fever, diarrhea, abdominal pain (arthritis, pharyngitis and septicemia as sequelae)
  - *Yersinia enterocolitica* primarily targets the ileum, inducing mucosal ulcerations, Peyer’s patch necrosis and mesenteric lymphadenopathy. A large inoculum dose (>10⁹ bacteria) may be required to initiate infection. Although the appendix is generally normal or only mildly inflamed upon histologic examination, the abdominal pain associated with *Y. enterocolitica* infection (as well as *Y. pseudotuberculosis* [see below], and less frequently *Campylobacter* and *Salmonella* infections) may mimic appendicitis (“pseudoappendicitis”).
* Most cases are foodborne.
  - There was a famous outbreak in Oneida County, NY in 1976 in which 218 school children were infected via chocolate milk. (13/218 children underwent appendectomy!) Contaminated chocolate syrup was added after pasteurization of the milk, and like *Listeria*, *Y. enterocolitica* can grow at refrigerator temperatures. (A *Yersinia* outbreak associated with pasteurized milk [and ice cream] also occurred in 2011 in Pennsylvania.)
  - Infections have also been reported in association with consumption of chitterlings (“chittlins”), large intestines of swine that are prepared around the Thanksgiving and Christmas holidays. While consumption of chittlins is particularly common in the southern U.S., an outbreak of yersiniosis associated with chittlins among children in Chicago in 2002 illustrates the fact that these infections can occur anywhere.

**The role of dogs:**
* Reports suggest that 1-6% of healthy dogs (and, to a lesser degree, cats) may be shedding *Y. enterocolitica*.
* Infection in dogs is generally subclinical, but they can have bloody diarrhea.
* Epidemiologically, human cases have been linked to households in which dogs were shedding the organism.

**Yersinia pseudotuberculosis**

**Disease in humans:**
* Mesenteric lymphadenitis with abdominal pain and nausea is the most common manifestation of human infection with *Y. pseudotuberculosis*, but abdominal aortic aneurysm and dermatologic conditions, including erythema nodosum and erythema multiforme, have also been reported.
**Disease in cats:**
* Infection causes a systemic, pyogranulomatous disease. (Ddx - FIP)
  - Disease also occurs in rabbits, guinea pigs, swine and turkeys.
* It is unclear if animals serve as a direct zoonotic risk, but they (especially rodents) can certainly contaminate the environment and foods.

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**Cutaneous larva migrans (CLM)**

This condition is caused by infection with the larvae of one of the **hookworms** of dogs and cats.
- *Ancylostoma braziliense* (most common), *A. caninum*, and *Uncinaria stenocephala* (least common)

* The infectious larvae are acquired from contaminated soil. The larvae **directly penetrate a person’s skin** and cause a highly pruritic, **“creeping eruption”** or “ground itch,” with raised, red “tracks” and vesicles.
  - *A. braziliense* often produces dramatic, long migratory tracts/lesions. The other hookworms tend to cause shorter lesions.
  - Systemic eosinophilia is less common than with visceral larva migrans (see below).
* The lesions generally regress spontaneously, but can be treated successfully with ivermectin (or albendazole, thiabendazole).

  - **Human eosinophilic enterocolitis** - Rarely, hookworm larvae (*A. caninum; A. ceylanicum* [tropics]) undergo a systemic migration to the GI tract in humans, leading to a syndrome of acute abdominal pain, anorexia, nausea and diarrhea called **human eosinophilic enterocolitis**. Ulceration of the terminal ileum and colon occurs, along with an eosinophilic inflammatory response. Interestingly, patients generally do not have premonitory CLM lesions.

**Visceral larval migrans (VLM)**

This can be a more serious disease (when clinically evident – often asymptomatic) associated with **systemic migration of roundworm larvae**, especially *Toxocara canis* (much less commonly *Toxocara cati*). *Toxocara canis* infections are extremely common (up to 90-100%) in puppies less than 3 months of age, and can also occur in older dogs. Furthermore, infected puppies can shed hundreds of thousands of eggs/defecation.

* VLM occurs most commonly in young children with poor hygiene practices and “pica” that allow for consumption of infective eggs from soil or contaminated foods or playthings.
* VLM is characterized by fever, malaise, wheezing and hepatomegaly, as well as a prominent leukocytosis, eosinophilia and hypergammaglobulinemia.
  - VLM severity ranges from asymptomatic (nearly 14% of the US population are sero [+]) based on a 2007 study from the CDC) to fatal.
- The larvae migrate from the GI tract to the liver via the portal circulation, then to the lungs and into the systemic circulation to reach virtually any organ in the body.
* As with CLM, visceral disease may resolve spontaneously, but can be treated with anthelmintics (albendazole, mebendazole), generally accompanied by corticosteroids to prevent intense inflammatory reactions to the killed larvae.

- **Ocular larva migrans (OLM):** In most cases, OLM develops in the absence of other signs of visceral involvement and in the absence of peripheral eosinophilia, and can present clinically up to 10 years after initial infection. Manifestations may include (generally unilateral) retinal granulomas, retinal detachment and endophthalmitis and “diffuse unilateral subacute neuroretinitis syndrome” (“unilateral wipeout syndrome”) with vision loss, vitritis and papillitis. OLM deserves special mention because of the sad fact that the posterior chamber masses of OLM have been **misdiagnosed as neoplasia (retinoblastoma), resulting in needless enucleation of children’s eyes.** One study in Ireland estimates that OLM occurs in about 6.6-9.7/100,000 persons. A survey of ophthalmologists in the US revealed 68 cases of OLM in 2009-2010, 68% of whom suffered permanent vision loss.

**Prevention:**
* In cutaneous and visceral/ocular larva migrans, the larvae involved must embryonate (most commonly in soil) for a period of days before they are infectious. Hence, transmission to humans is not typically associated with direct animal-human contact (although a recent study has shown that dogs may carry embryonated eggs on their hair coats). Veterinarians have an important public health responsibility to advise their clients of the zoonotic potential of these common nematodes and to control these parasites at the individual pet and, ultimately, at the population level, through consistent programs of fecal testing and anthelmintic treatments. Unfortunately, in one survey, **fewer than 1/3 of veterinarians discussed the zoonotic aspect of these parasites with their clients.**
* Since virtually all puppies are infected from the dam, the CDC recommends that all puppies be wormed beginning at 2 weeks of age (much earlier than routinely recommended by most practicing veterinarians) and that the dams be treated simultaneously.
* **Every owner of a new puppy (or kitten) should be advised of the zoonotic potential of these parasites and the importance of their control.**

**Baylisascaris procyonis** larva migrans

“Baylis” (H.A. Baylis was a parasitologist in the British Museum in the early 20th century.) + “askaris,” Greek for intestinal worms. (Gavin et al. 2005) **Baylisascaris procyonis** is the common roundworm of raccoons. It causes a recognized larva migrans of other wild animals that serve as intermediate hosts (affecting at least 90 species including rodents, birds, rabbits, foxes, weasels, otters, badgers), usually leading to neurologic disease. This parasite is also a serious zoonotic concern for humans.

* Young raccoons, and humans and other intermediate hosts, become infected by ingesting eggs containing larvae from soils contaminated with raccoon feces, whereas adult raccoons become infected by ingesting larvae imbedded in the tissues of intermediate hosts.
  - Infection is very common in raccoons (51-82% seropositivity among raccoons tested in IN, IL and WI; 22% of raccoons in urban Atlanta infected; 16-32% of raccoon latrines in CA contained infective eggs). Infected raccoons can shed millions of eggs/day. The eggs embryonate and become infectious about 2-4 weeks later.
  - Kinkajous (“honey bears”), exotic procyonids sometimes kept as pets, can also be infected.
  - Dogs can be infected as an aberrant host and can shed eggs in their feces.
- Cats appear to be relatively resistant to infection.
- The eggs are extremely hardy in the environment. Experimentally, inactivation does not occur until heating in water to 62°C or dessication for 7 months. Freezing to -15°C for 6 months did not inactivate the eggs; successful disinfection of soil may require flaming.

**Disease in humans:**
* As with traditional VLM, infections in humans are often linked to pica behavior and, therefore, occur most commonly in children.
* *B. procyonis* larvae have a **predilection for migration through the CNS** in people, as in other intermediate hosts.
  - Approximately 5-7% of the larvae invade the brain and, because of their large size (up to 2mm in length) and the intense inflammatory response generated, a great deal of tissue destruction occurs. Encephalitis is accompanied by peripheral and CSF eosinophilia.
  - Although only ~30 cases are documented in the literature, illness is often severe. In a study of 14 documented cases of *Baylisascaris* encephalitis in the U.S., 5 of 14 were fatal and survivors generally had severe long-term neurologic sequelae (only 1 of 14 cases ended in full recovery). Unfortunately, because the damage can occur before the onset of clinical signs, treatment (typically albendazole + corticosteroids) is of limited efficacy. This parasite has even been suggested to have potential use as a bioterrorism weapon.

**Strongyloides stercoralis larva migrans**

Animals are a more direct threat to humans with this nematode than others because the eggs of *Strongyloides* are embryonated and infectious as soon as they're passed, rather than requiring a prolonged period of development in the soil!

**Disease in humans:**
* People are infected by cutaneous penetration of infectious larvae. The larvae then migrate to the GI tract, producing abdominal pain, diarrhea, nausea and potentially a protein-losing enteropathy and weight loss.
* The most **severe disease occurs in immunocompromised patients due to “hyperinfection” or “autoinfection”** (infectious larvae re-infect people via the lower perineum or within GI tract before they've exited the body). In these patients, the infestation may be **fatal**.

**Echinococcus spp. tapeworm disease**

Dogs and wild canids are the definitive hosts for the most common forms of *Echinococcus* tapeworms. These tapeworms also pose a very significant public health risk. **People become aberrant intermediate hosts for Echinococcus** and develop destructive tissue cysts by ingesting eggs that have been passed by canids into the environment. The oncosphere larvae are released from the eggs in the GI tract and spread via the blood stream or lymphatics to internal organs.

* **There are two primary species of Echinococcus**, each associated with specific definitive and intermediate hosts and pathologic lesions:
  - *E. granulosus* infections in humans produce unilocular “**hydatid cysts**.”
    -- This parasite is found worldwide. In the U.S., *E. granulosus* is most prevalent in the sheep-raising areas of the western U.S., where sheep normally serve as the intermediate host and domestic dogs are the most common definitive host. There are also sylvatic cycles involving wild canids and cervids (reindeer, moose).
Hydatid cysts are slowly enlarging, fluid-filled, space-occupying lesions producing pain and potentially physical obstruction/pressure on surrounding organs. They develop over a period of months to years. If the cyst ruptures, “daughter” cysts may be released and spread elsewhere in the body. The cysts most commonly develop in the liver (or lungs). Lesions in the liver may cause secondary cholestatic liver disease.

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It may be possible to vaccinate dogs against *E. granulosus* using recombinant parasite proteins.

- **E. multilocularis** infections in humans produce “alveolar hydatids.”
  -- This parasite is found primarily in northern climes. In the U.S., *E. multilocularis* is most prevalent in the North Central states, Canada and Alaska. Rodents serve as the normal intermediate hosts and wolves and coyotes are the most common definitive hosts. However, domestic dogs are increasingly being implicated as definitive hosts in Alaska, and there is great concern for further southward progression of this parasite and extension into the domestic dog population of the continental U.S.
  -- Compared to hydatid cysts, alveolar hydatids are **much more aggressive lesions** in which the organism reproduces asexually by lateral budding and tumor-like infiltration into surrounding tissues, rather than into the cyst itself. **Fatality rates can approach 50%,** although subclinical exposure can also occur.

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Additionally, a less frequently diagnosed form of echinococcosis is polycystic echinococcosis associated with *E. oligarthrus* (definitive host is wild and domestic felids) and *E. voegli* (definitive host is the bush dog). Both occur primarily in South America.

* Diagnosis of human *Echinococcus* infections is made by imaging the lesions, and/or by detection of circulating parasite antigens or antibodies.
  - Treatment of hydatid cysts in humans may be medical or surgical, depending on the extent and accessibility of the lesions. Prior to surgical excision, the lesions are often aspirated and sometimes injected with a protoscolicidal agent (e.g., 70-95% alcohol) to reduce the chance for leakage of anaphylactogenic or infectious contents during surgery. This “PAIR” approach (puncture, aspiration, injection, re-aspiration) can sometimes be used in lieu of surgery. Finally, albendazole and mebendazole, sometimes combined with praziquantel, are often used together with surgery or PAIR, or as the sole therapy in cases of inoperable lesions.

* **The eggs of Echinococcus spp. cannot be differentiated from those of the common *Taenia* tapeworm of dogs.** Therefore, in endemic areas, any *Taenia*-like eggs should be considered possible evidence of *Echinococcus* infection.
  - Luckily, praziquantel is highly effective against this tapeworm, as well as *Taenia* in dogs. (See McManus et al. [2003] and Eckert and Deplazes [2004] for excellent reviews of *Echinococcus* disease)

### Canine whipworm infection of human beings

People have their own whipworm, *Trichuris trichuria*, but people are also infrequently infected with the canine whipworm, *Trichuris vulpis* (most commonly children or those with pica). Infections may be asymptomatic or may involve diarrhea, nausea, and abdominal pain.

* **Dirofilaria larva migrans**

Although well known as the heartworm of dogs, *Dirofilaria immitis* can also be transmitted to people, leading to a larva migrans syndrome. It should be stressed, however, that **dogs are not a direct zoonotic threat. Transmission to people, like dogs, occurs via mosquitoes.** However, the presence
of a heartworm (+) dog in the immediate environment could theoretically increase the chance for human contact with infected mosquitoes.

* In people, infection is asymptomatic in 50% of cases, but may induce inactive, coin-sized lesions on chest radiographs. When present, clinical disease may include coughing, chest pain and hemoptysis.

- People can also be infected with *D. repens* (dog reservoir) and filarids of other species, such as raccoons, bears and porcupines, usually leading to the formation of subcutaneous inflammatory masses (and in one case concomitant meningoencephalitis with *D. repens* infection).

References


Q-Fever

Coxiella burnetii

The name Q fever comes from the word “query,” reflecting the unknown etiology of the disease when it was first recognized in Queensland, Australia in 1935. In the U.S., human Q fever has been reported most
frequently from California. *Coxiella burnetii* is a rickettsial-like organism that is maintained in bird and rodent reservoirs in nature. Transmission among these natural reservoir species occurs primarily via *ticks*. Over 40 species have been implicated, and transmission may occur even just via inhalation of tick excreta deposited on animal wool. Transmission from wild animals to domestic animals is poorly understood. Domestic animals may initially contract the infection via ticks, but likely spread it between themselves thereafter via aerosols, direct contact or mechanically via flies.

* *Coxiella burnetii* can be extremely infectious for humans* - just a single organism is sufficient to initiate infection with certain strains of the organism, and the LD$_{50}$ for non-human primates can be as low as 1.7 organisms.

* A study of seroprevalence of veterinarians tested at the 2006 AVMA convention found a seropositivity rate of 22% among the 508 veterinarians tested, with highest rates among those in mixed animal or large animal practice.

* Sheep are the most common source of infection for humans.
  - The organism replicates to very high levels in the placenta (up to $10^9$ infectious doses per gram of tissue) and is then shed in the reproductive tract fluids at parturition.
    -- Sheep (cattle and goats) may abort because of placentitis, or they may simply be infected subclinically.
  - Infected animals also shed the organism in urine, feces, and milk.
  - Remarkably, a study published in 2005 found that 94% of 316 bulk tank milk samples in the U.S. tested PCR positive for *C. burnetii*, suggesting that this organism is far more prevalent in the U.S. than generally considered.
    -- Thankfully, however, cases of clinical illness in people in the U.S. remain limited, with approximately 20-70 cases per year.

* Some of the more interesting zoonotic cases of Q fever have involved contact with parturient cats (people playing poker in the room where a cat was giving birth!) and dogs (there have been at least 2 family outbreaks associated with dogs).* In each case, a portion of the litter died shortly after birth, although as with ruminants, infections in dogs and cats are most often subclinical. Estimates of seropositivity rates for dogs and cats range from 1-66% (most commonly 15-20%), depending on the population surveyed. In 2005, 110 school students in Israel developed Q fever, possibly due to the presence of a parturient cat in their school dining room.

**Clinical symptoms of Q fever in humans:**
* Infection most commonly occurs via inhalation while assisting at parturition, and serologic studies suggest that infections may be more common than recognized, with many self-limiting infections. However, people can also be infected (and were prior to pasteurization) by ingestion of unpasteurized milk or even just inhalation of the organism from milk.
  - *Coxiella burnetii* is very resistant to heat and drying, and thus can be maintained in the environment. As such, human cases are not always clearly linked to direct animal exposure.
* Q fever can present as an acute febrile disease with malaise, myalgia, headache, chills and sweats, with pneumonia (with coughing) and/or hepatitis, and chronically as endocarditis (especially in people with underlying valvular disease), pericarditis, hepatitis, meningoencephalitis, optic neuritis, or osteomyelitis/arthrits.
  - Mortality is <1% if appropriately treated with tetracyclines, but can be in excess of 50% without therapy.
* Reports of human-to-human transmission are extremely rare, but *C. burnetii* has been isolated from human milk and human placental tissues, and there are reports of transmission to physicians during abortion procedures and autopsies.
Leptospirosis

*Leptospira interrogans, Leptospira kirschneri*

There are more than 250 “serovars” of *Leptospira* bacteria. The pathogenic serovars do not replicate outside animal hosts, and human-to-human transmission is rare.

*Animals are critical to the maintenance of pathogenic leptospires in a given area. They persist in the renal tubules of animals without causing disease, and can be excreted in the urine for prolonged periods of time. (Leptospires evade immune responses while sequestered in renal tubules.) Specific serovars are “hosted-adapted” to certain reservoir species and generally do not cause disease in those hosts, e.g.:
- *L. interrogans canicola* /dogs
- *L. interrogans icterohaemorrhagiae* /rats
- *L. kirschneri grippotyphosa* /voles, raccoons and other small mammals
- *L. interrogans bratislava* /pigs and rats and other small mammals

* Rats are the most common source of infection for humans worldwide. In the U.S., however, the most common sources of infection for humans are DOGS (increasingly even in suburban areas) > LIVESTOCK > rodents > other free-ranging mammals (including squirrels, skunks, raccoons, opossums, seals, and sea lions [major outbreak among sea lions along the Pacific Northwest coast in 2004]).

**Leptospirosis in people:**

* Leptospirosis can occur as either sporadic cases or in epidemics. Humans are susceptible to infection with a variety of serovars. In the U.S., about half of the 100-200 cases/year occur in Hawaii.
  - Globally, the incidence of leptospirosis is highest in tropical areas, especially when heavy rainfall drives rodents into urban dwellings and increases risks for waterborne infection. Examples include:
    -- Thailand, 2000: massive outbreak associated with flooding, more than 5,000 people infected and over 180 died; India, 2005: over 100 people died in just 2 days, Mumbai after heavy rains the prior month

* Infection occurs through mucosal contact with water or soil contaminated with the urine of infected animals. Leptospires can survive in moist environments for months, but are killed by freezing.
  - Occupations at risk include sewer workers (“sewerman’s flu”), members of the military working in water (“swamp fever”), rice and sugar cane plantation employees (“cane-cutters fever, rice-field fever”), and farmers/veterinarians (“swine herder’s disease”).
  - Veterinarians, farmers and abattoir workers are at particularly heightened risk.
    -- In one survey, 15% of abattoir workers were seropositive, and the rate of seropositivity was directly proportional to their number of years on the job!
    -- As veterinarians, we should handle even routine urinalysis specimens as if they contain leptospires, taking precautions such as gloves and a face shield (to prevent mucosal splashes). Similar precautions should be taken by animal staff when hosing down dog runs, etc.
* Increasingly, leptospirosis is associated with recreational activities, e.g., kayaking or swimming in contaminated waters, triathlons, eco-challenge races, etc. (Doxycycline may be preventative for those taking part in eco-challenges.)

* Clinically, human infections with *Leptospira* begin, after an incubation period of 7-12 days, with fever (biphasic) and “flu-like” illness. Patients may then develop intense headaches, severe myalgia, abdominal pain, nausea, diarrhea, and sometimes rash, conjunctivitis/uveitis and conjunctival hemorrhage.

  - “Weil’s disease” (most commonly due to infection with *L. icterohaemorrhagiae*) is the name for the form of leptospirosis (~10% of cases) characterized by severe hepatic and renal disease associated with hepatomegaly, jaundice and renal insufficiency. Recovery can take months and mortality can approach 20% if liver/renal compromise is not treated aggressively.
  
  -- Weil’s disease has recently been implicated in massive die-offs of Native Americans in Massachusetts in 1616-1619 (historical records suggest epistaxis and jaundice).

  - The less severe, anicteric disease comprises ~90% of human cases.
    
    - Aseptic meningitis can occur as a sequela of either Weil’s disease or anicteric leptospirosis. The meningitis is thought to be immune-mediated, since the organism is generally not present in the CSF by the time clinical signs develop.

  - *Leptospira* infections affected about 2,500 and killed at least 16 people in Nicaragua in 1995 in an outbreak of what was initially called "Mystery Disease,” now called “severe pulmonary hemorrhage syndrome” (SPHS).

    -- This outbreak occurred following a period of substantial flooding, and specific risk factors for infection included walking in creeks, having household rodents and owning dogs with *Leptospira* titers >400.

    -- The unique feature in these cases was a syndrome of pulmonary hemorrhage. This is a rare manifestation of leptospirosis. However, similar cases have been reported in Asia (Korea, China); Argentina in 2000-2001; Brazil in 2003-2005; Greece since 1999.

    -- It remains unclear whether this form of disease is associated with a specific clone/genotype of *Leptospira* organism.

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**Leptospirosis in animals:**

* Cattle, swine:
  - reproductive disorders; multivalent vaccines are used for control.

* Horses:
  - The most common manifestation of *Leptospira* infection in horses is recurrent uveitis. This has historically been thought of as an immune-mediated disorder that develops 12+ months after infection, and it has been suggested that the basis for this immune reaction is antigenic cross-reactivity between a 90kD *Leptospira* protein and a protein in the equine cornea.

  - Abortions have been reported to be associated with *Leptospira* infections in horses. For this reason, some horse breeders are using the cattle vaccine (off-label use) in horses.

    -- The horses are seropositive to *Leptospira*, and the fetuses have histopathologic lesions and silver-staining organisms in tissues consistent with *Leptospira*, but the organism has not been recovered in culture.

* Dogs:
  - Many, if not most, *Leptospira* infections in dogs are subclinical.

  - When infections are clinically apparent, the typical presentation is one of fever, anorexia and vomiting that progresses to hepatic disease and hemorrhages (petechiae and ecchymoses).

    -- This acute form of hepatic and hemorrhagic disease is most often associated with infection with *L. icterohaemorrhagiae*. The coagulation abnormalities may be due to: reductions in the production of clotting factors because of hepatic failure; *Leptospira* LPS-stimulation of platelet activation; and, *Leptospira*-induced vasculitis and endothelial cell damage.
The overall prevalence of leptospirosis in dogs in the U.S. and Canada has increased since 1983, according to a large study of nearly 2 million canine patients examined at veterinary medical teaching hospitals. Dogs at greatest risk according to this study were male herding dogs and other working dogs, and hounds. However, leptospirosis has also been documented in household pets (e.g., outbreak near Detroit in 2011). German Shepherd dogs may be at increased risk.

**A NOVEL FORM OF LEPTOSPIROSIS, PRESENTING AS ACUTE RENAL FAILURE (ARF) with fever, anorexia, lethargy, vomiting, polyuria and polydypsia, and sometimes abdominal pain, has been identified in dogs.**

-- This syndrome has most often been associated with infection with *L. grippotyphosa*, *bratislava* and/or *pomona*, not the “typical” canine leptospires, *L. icterohaemorrhagiae* and *L. canicola* (although a one study found that *L. bratislava* did not infect experimentally inoculated dogs). The infections may be characterized by **unique ultrasonography and histopathology findings in the kidneys**, but the infection may also involve the liver. These cases have occurred primarily in the **fall** of the year.

--- Interestingly, acute renal failure in a person has also been linked to *L. grippotyphosa* infection.

--- IV penicillin first to eliminate the leptospiremia (approximately 2 weeks of therapy), followed by 2-3 weeks of oral doxycycline to reduce the leptospiuria.

--- ARF with oliguria/anuria predicts a poor prognosis.

--- A study of over 23,000 dogs in the U.S. sampled between 2002-2004 found that seropositivity rates are now highest to *L. grippotyphosa* and *L. autumnalis*.

* Cats: infection and disease are very rare

* Sea lions: leptospirosis sickened dozens of sea lions in California in 2008 and again in 2010 in Oregon, and has previously been documented in harbor seals and fur seals. Additionally, researchers studying/performing necropsies on sea lions have been infected.

**Diagnosis of Leptospira infection in animals:**

* darkfield microscopy of urine (but absence of organisms by dark-field does NOT rule-out infection)

* culture (or FA, PCR or Ag-capture ELISA identification) of *Leptospira* organisms in blood (early in the course of disease) or urine (after the first week of illness - pretreatment with furosemide may increase the recovery of organisms in urine)

--- It is important that culture samples be collected prior to initiating antibiotic therapy!

--- Routine urine culture should also be conducted in cases of ARF to rule-out non-*Leptospira* pyelonephritis.

* histopathology (silver staining for the organism)

* serology (microscopic agglutination test [MAT] most commonly)

--- As a guide, vaccine titers in dogs rarely exceed 1:400 and generally decrease to ~1:100 by 2-3 months after vaccination.

**Vaccination of dogs:**

* *Leptospira* vaccines for dogs are now available in 2 forms. The original vaccines contained only the *L. canicola* and *L. icterohaemorrhagiae* serovars; vaccines have more recently become available against *L. grippotyphosa* and *L. pomona*. (The antibodies induced by the later vaccines may also be strongly cross-reactive with *L. autumnalis* in serologic testing.)

***It is very important to realize that vaccinated animals (dogs & livestock), though possibly protected from clinical disease, may still persistently shed these organisms in their urine and, therefore, serve as a source of infection for humans.***
References


