**Anthrax**

**Definition of the Problem**

The malicious distribution of anthrax spores through the mail in the United States during the fall of 2001 acutely heightened awareness of anthrax as a bioterrorist agent. However, anthrax has been recognized for thousands of years as a naturally occurring zoonotic disease of people exposed to infected animals or contaminated animal products. The 5th and 6th biblical plagues are thought to have been systemic and cutaneous anthrax, respectively, Virgil described outbreaks of anthrax-like disease among people and animals in Rome in 70 BC, and references were made repeatedly to anthrax in the “Hippokratika,” a series of writing about animal health that was produced in the 900s AD. Finally, this disease is famous in the history of science because Koch’s postulates were defined in 1876 using anthrax as the model infection.

**The Etiologic Agent.** *Bacillus anthracis* is a large, Gram (+) bacillus with characteristic square ends. The name “anthracis” comes from the Greek word “anthrakis” meaning “coal.” This name refers to the blackened “eschar” skin lesions that typify cutaneous anthrax in humans. *Bacillus anthracis* will grow well on standard blood agar medium. When growing vegetatively in vitro, *B. anthracis* is characteristically found in long chains that can be easily appreciated on a simple Gram stained smear of the organism. Additional identification is based upon biochemical tests, characteristic spore formation (see below), bacteriophage lysis and/or fluorescent antibody labeling.

**Spore Formation.** *Bacillus anthracis* produces extremely resistant endospores when exposed to oxygen in the environment. These spores, not the vegetatively growing bacteria, are the most important unit of infection. As an indication of how environmentally resistant these spores are, they have been recovered from 200+ year-old remains in archeological digs, they are resistant to microwave irradiation at 100°C in water for 30 min and they are resistant to conventional pasteurization (although they would likely be killed by ultrapasteurization).
Pathophysiology and Clinical Presentation

Pathogenesis. Following deposition of *B. anthracis* spores in the body (either through a skin wound or via ingestion or inhalation), germination occurs and vegetative growth begins. The germination process usually occurs quickly, consistent with the typical incubation period of 2-7 days. However, if the spores are inhaled and carried to mediastinal lymph nodes, germination may be delayed as long as 60 days. In cases of systemic infection, *B. anthracis* spreads rapidly from the initial site of replication via lymphatics and the bloodstream to colonize tissues throughout the body. A high level bacteremia develops, eventually overcoming the ability of the spleen to filter out the organism. The ability of *B. anthracis* to avoid killing by phagocytic cells is enhanced by the presence of a D-glutamyl polypeptide capsule. The lesions of anthrax are caused by the coordinate action of 3 toxin components expressed by *B. anthracis*: edema factor (EF), lethal factor (LF) and protective antigen (PA). PA binds to a Type-I membrane protein on cells, is cleaved by a furin-like protease, and then heptamerizes to produce a receptor molecule to which either LF or EF can bind. Once this complex is enveloped in an endosomal compartment, the low pH causes a conformational change in the structure of PA that allows it to insert into the cell membrane and form a pore through which LF or EF can enter the cell’s cytoplasm. LF is a protease that induces macrophage death, with release of massive quantities of inflammatory mediators. EF is an adenylate cyclase that increases cAMP levels and ultimately leads to fluid loss from cells. Together these actions cause the edema, hemorrhage and necrosis that typify anthrax. It should also be noted that because of this toxin-based pathogenesis, antibiotic therapy can only be effective if initiated before extensive toxin production has occurred.

Clinical Disease in Humans. Anthrax in humans occurs in three primary forms.

Cutaneous Anthrax develops when spores are deposited in breaks in the skin. The lesions are unique, beginning as a pruritic papule or macule, progressing through an ulcer stage with surrounding vesicles, and ultimately becoming a painless, black, necrotic eschar. Over 1-2 weeks, the dried eschar dislodges. There may also be fever, lymphadenopathy and malaise along with the cutaneous lesions. The case fatality rate in patients with cutaneous anthrax who are not treated with antibiotics can be as high as 20%.

Inhalational Anthrax occurs following aerosol exposure and deposition of anthrax spores in the lungs. A flu-like presentation develops initially, with symptoms such as fever, chills, sweats, malaise, headache, dyspnea and abdominal pain and nausea. This period of illness (lasting several hours to several days) may be followed by a short period of apparent recovery before the second stage of fever, dyspnea, hypotension and shock develops. At this point, moist rales may be evident upon auscultation, and pulmonary infiltrates and pleural effusion may be detected radiographically. In addition, massive mediastinal lymphadenopathy, mediastinal hemorrhage and radiographic evidence of mediastinal widening are classic findings in inhalational anthrax. Historically, the case fatality rate with occupationally-acquired inhalational anthrax was 89%. However, with advances in critical care and shock therapy, survival rates can be substantially increased, as evidenced by the successful treatment of 6 of 10 patients in the recent bioterrorist-related cases of inhalational anthrax. Finally, it should be noted that anthrax is not highly contagious via person-to-person transmission, even in cases of inhalational anthrax.
**Differentiating Inhalational Anthrax and Influenza.** In the initial stage, inhalational anthrax may be clinically similar to influenza. To help differentiate the two diseases, the CDC has developed the following guidelines.

### Table 1. Symptoms and Signs of Inhalational Anthrax, Laboratory-Confirmed Influenza, and Influenza-Like Illness (ILI) From Other Causes.

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Inhalational Anthrax (n=10)</th>
<th>Laboratory-Confirmed Influenza</th>
<th>ILI From Other Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Temperature</td>
<td>70%</td>
<td>68%–77%</td>
<td>40%–73%</td>
</tr>
<tr>
<td>Fever or Chills</td>
<td>100%</td>
<td>83%–90%</td>
<td>75%–89%</td>
</tr>
<tr>
<td>Fatigue/Malaise</td>
<td>100%</td>
<td>75%–94%</td>
<td>62%–94%</td>
</tr>
<tr>
<td>Cough (Minimal or Nonproductive)</td>
<td>90%</td>
<td>84%–93%</td>
<td>72%–80%</td>
</tr>
<tr>
<td>Shortness of Breath</td>
<td>80%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Chest Discomfort or Pleuritic Chest Pain</td>
<td>60%</td>
<td>35%</td>
<td>23%</td>
</tr>
<tr>
<td>Headache</td>
<td>50%</td>
<td>84%–91%</td>
<td>74%–89%</td>
</tr>
<tr>
<td>Myalgias</td>
<td>50%</td>
<td>67%–94%</td>
<td>73%–94%</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>20%</td>
<td>64%–84%</td>
<td>64%–84%</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>10%</td>
<td>79%</td>
<td>68%</td>
</tr>
<tr>
<td>Nausea or Vomiting</td>
<td>80%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>30%</td>
<td>22%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Adopted from *MMWR 2001; 50:984-986.*

**Gastrointestinal Anthrax.** Anthrax can occur following ingestion and deposition of spores in either the upper or lower gastrointestinal tract. In the oropharyngeal form, ulcers may form in the oropharynx or esophagus, and patients may exhibit fever, sore throat, dysphagia and regional lymphadenopathy. In the lower gastrointestinal tract, mucosal ulcers are most commonly present in the ileum and colon, along with a hemorrhagic enteritis. Patients may present with fever, nausea, hematemesis and bloody diarrhea, with progression to toxemia and hypotensive shock. As in inhalational anthrax, the case fatality rate for gastrointestinal anthrax may be as high as 75%.

**Meningitis.** A hemorrhagic meningitis can develop as a complication of any of the three primary forms of anthrax.

**Agricultural Factors**

Animals play a critical role in the epidemiology of anthrax in humans. Humans can be infected by direct contact with infected animals (veterinarians, farmers, abattoir workers), by occupational exposure to contaminated animal products (e.g., sheep and goat hides, “wool sorter’s disease”), by ingestion of meat from infected animals (milk can also contain the organism in the end stages of
disease), or by contact with soils that were contaminated by an infected animal. In the later regard, *B. anthracis* is found characteristically in specific regions in the world called “incubator zones,” “anthrax districts” or “cursed fields.” These are areas where animals die and contaminate the soils with spores that reinfect new animals in a cyclical pattern. Typically these incubator zones also have alkaline, high N$_2$ content soils and often alternating periods of rain and drought. High CO$_2$ levels in decaying bodies inhibit sporulation, but sporulation occurs as soon as the organism is exposed to O$_2$ outside the body.

Therefore, the bodies of animals suspected of having died of anthrax should not be opened for pathologic examination. Instead, a blood sample should be collected with as little contact with the carcass as possible (e.g., by cutting off the tip of the animal’s ear or incising the coronary band just above the hoof wall) and then the carcass should be burned thoroughly or buried deep and covered with calcium oxide quick lime. (Quick lime acts to pull water out of the carcass and thereby speed decomposition.)

Globally, anthrax is endemic in tropical and subtropical areas of India, Pakistan, the Middle East, Asia, Africa, South America and Haiti. In the United States, anthrax in animals continues to occur periodically in incubator zones in the Dakotas, Nebraska, Missouri, Oklahoma, Texas, Arkansas, Louisiana, Mississippi and parts of New Mexico and Minnesota. These incubator zones often coincide with old cattle drive trails such as the Sedalia cattle trail in Oklahoma. However, the occurrence of anthrax in cattle in Santa Clara, CA in 2001 points out that anthrax can appear anywhere that local conditions are conducive to perpetuation of spores in the soil.

In animals, *B. anthracis* is most commonly acquired by ingestion, but can also occur by inhalation or through wounds (even just insect bite wounds). Herbivores (e.g., cattle, sheep, goats, bison, deer, etc.) are most susceptible to disease, while pigs and carnivores (e.g., dogs and cats) are less susceptible. In cattle, peracute death is a common manifestation of anthrax. Hemorrhage may or may not be evident in these peracute cases. In less acute cases, cows can exhibit fever, anorexia, hematuria, hematochezia, peripheral edema, splenomegaly, respiratory distress and behavioral changes and seizures (reflecting CNS edema and hemorrhage). Bloody discharges can emanate from any orifice, blood in the body typically does not clot, and rigor mortis is often absent. In horses, infection often presents initially as colic and enteritis, followed by the development of edema, hemorrhage and death in 2-4 days. Pigs and dogs generally have a more limited course of disease manifest by gastroenteritis and/or pharyngeal edema. However, the pharyngeal edema may lead to death by asphyxiation.

In endemic areas in the world, animals can be vaccinated with an avirulent (live) spore vaccine (“Stern vaccine”). In incubator regions of some areas in the United States (e.g., the Dakotas), vaccination is also commonly practiced. However, in other areas (including Wisconsin), vaccination is only carried out by authority of the State Veterinarian. To the knowledge of these authors, naturally occurring anthrax has not been diagnosed in Wisconsin since the 1950s. However, over 150 livestock animals in North Dakota and 6 cows in Minnesota died or were euthanized because of anthrax in 2000. In this outbreak, 2 farmers slaughtered and consumed meat from one of the affected cows. One of these farmers developed intestinal anthrax and the other cutaneous anthrax. During 1997-2001, anthrax also occurred in animals in South Dakota, New Mexico, Texas and Nebraska.
Management Issues for Human Health

**Diagnosis.** The clinical diagnosis of anthrax in humans requires a high degree of suspicion. Healthcare workers taking care of persons with any of the clinical findings summarized above should immediately notify their local or state health departments. In particular, the sudden appearance of several cases consisting of an acute febrile illness that result in a fulminant course and death should be considered a public health emergency.

For inhalation and gastrointestinal anthrax, obtaining standard blood cultures is the most useful clinical test because growth is typically present within 6-24 hours. However, 1 or 2 doses of antibiotics may result in negative cultures. Therefore, blood cultures should be obtained prior to initiation of any antibiotic therapy. In 2001, each of the 8 patients who had blood cultures obtained prior to initiation of antibiotics had positive blood cultures. If the microbiology laboratory is alerted to the possibility of anthrax, biochemical testing together with an assessment of colony morphology may provide a preliminary diagnosis within 12-24 hours of blood culture inoculation. In contrast, many clinical laboratories may misidentify the organism if laboratory personnel are not notified of the possibility of anthrax. This is because the isolation of *Bacillus* species most often represents contamination with the common organism *Bacillus cereus*. Therefore, definitive diagnosis by a clinical reference laboratory is recommended when anthrax is suspected. In the United States, a laboratory response network (LRN) has been established through a collaboration of the Association of Public Health Laboratories and the CDC. Currently 81 clinical laboratories in the LRN can diagnose bioweapons pathogens such as *B. anthracis*.

Because inhalation anthrax is not a true pneumonia, sputum culture and Gram stain are unlikely to be diagnostic. Similarly, nasal swabs results are considered unreliable and should not be used as a clinical diagnostic test. If obtained as part of an epidemiology study to ascertain the possibility of exposure, the results of a nasal swab should not be used to rule out infection with *Bacillus anthracis*. In contrast a positive sputum culture or nasal swab should prompt the initiation of antibiotic therapy. If cutaneous anthrax is suspected and vesicles are present, a Gram stain and culture of fluid from the vesicles should be obtained. If the Gram stain is negative, the patient is already on antibiotics, or there are no vesicles, then a punch biopsy should be performed. The biopsy specimen should be sent to a laboratory capable of performing immunohistochemical staining or polymerase chain reaction assays. Blood cultures should be obtained and antibiotic therapy begun pending the laboratory results. Antibodies to the protective antigen (anti-PA IgG) are helpful in determining past exposure; however, they should not be used as a diagnostic test for acute anthrax infection. The following algorithms, adapted from CDC recommendations, summarize the clinical management of human anthrax.
Clinical Algorithm for Cutaneous Anthrax

Typical appearance and progression of cutaneous anthrax:
- Painless or pruritic papule/pustule
- Vesicular or ulcerative lesion
- Black eschar

Obtain diagnostic tests:
- Gram stain and culture of skin lesion
  - Unroofed vesicle fluid (dry swab)
  - Base of ulcer (moist swab)
  - Edges of or underneath eschar (moist swab)
- Obtain blood cultures
- Consider skin (punch) biopsy if patient in on antimicrobial drugs OR if gram stain and culture are negative for *B. anthracis* and clinical suspicion remains high
- Start empiric therapy for cutaneous *B. anthracis*
- Notify public health authorities

Culture negative and no progression of papule to eschar, cutaneous anthrax unlikely and tx may be stopped

Culture positive

Progression to eschar

Continue antimicrobial therapy

*Adopted from MMWR 2001; 50:941-948.*

**Treatment.** Most natural strains of *B. anthracis* are exquisitely sensitive to penicillin, which has historically been the drug of choice to treat anthrax. Doxycycline has also been used and has proven efficacy in monkey trials of the disease. Animal studies also suggest excellent efficacy for ciprofloxacin. However, there is concern that bioweapon strains of the organism have been engineered to be resistant to both the penicillin and tetracycline classes of antibiotics. In 2001, the clinical isolates from patients with inhalation anthrax in the United States were found to be susceptible to penicillin, doxycycline, and ciprofloxacin. However, the isolates were found to have an inducible β-lactamase in addition to a constitutive cephalosporinase. Although the clinical importance of this finding is
unknown, the theoretical concern of resistance was high enough that CDC advised against the use of monotherapy with either penicillin or amoxicillin for anthrax. The Working Group on Civilian Biodefense has recently updated the management recommendations for anthrax associated with a bioterrorism attack.

The following tables reflect these up-to-date recommendations for the treatment of inhalation and cutaneous anthrax as well as post-exposure prophylaxis for exposure to spores of *B. anthracis*.
**Module VI**

**Partners in Agricultural Health**

### Table 3. Recommended Therapy for Inhalational Anthrax Infection in the Contained Casualty Setting*

<table>
<thead>
<tr>
<th>Category</th>
<th>Initial IV Therapy††</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Ciprofloxacin, 400 mg every 12 h or Doxycycline, 100 mg every 12 h and 1 or 2 Additional antimicrobials*</td>
<td>IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg twice daily or Doxycycline 100 mg twice daily Continue oral and IV treatment for 60 d</td>
</tr>
<tr>
<td>Children</td>
<td>Ciprofloxacin, 10-15 mg/kg every 12 h††† or Doxycycline††† for those aged &gt;6 y and weight &gt;45 kg: 100 mg every 12 h; &gt;6 y and weight &lt;45 kg: 2.2 mg/kg every 12 h; &lt;6 y: 2.2 mg/kg every 12 h and 1 or 2 Additional antimicrobials*</td>
<td>IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 10-15 mg/kg every 12 h††† or Doxycycline for those aged &gt;6 y and weight &gt;45 kg: 100 mg twice daily &gt;6 y and weight &lt;45 kg: 2.2 mg/kg twice daily &lt;6 y: 2.2 mg/kg 2 daily Continue oral and IV treatment for 60 d†††</td>
</tr>
<tr>
<td>Pregnant women††</td>
<td>Same as for nonpregnant adults</td>
<td>IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate‡‡; oral therapy regimens are the same for nonpregnant adults</td>
</tr>
</tbody>
</table>

*Immunocompromised persons. Same for nonimmunocompromised adults and children

†This table is adapted with permission from *Monthly and Mortally Weekly Report.* For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.

*†Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.

‡Streptococci may be considered as an adjunctive therapy for patients with severe odemat and for meningitis based on experience with bacterial meningitis of other etiologies.

§Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, ciprofloxacin, and clindamycin. Because of concerns of contribute to inducible β-lactamase in Bacillus anthracis, penicillin and ampicillin should not be used alone. Consultation with an Infectious Disease specialist is advised.

‖Initial therapy may be altered based on clinical course of the patient; 1 or 2 antimicrobial agents may be adequate as the patient improves.

¶Meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.

‖If intravenous (i.v.) ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing but may not be achieved if vomiting or fever is present.

‖In children, ciprofloxacin dosage should not exceed 1 g/d.

||The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (e.g., Rocky Mountain spotted fever).

**Adapted from JAMA 2002; 287:2236-2252.**

### Table 4. Recommended Therapy for Inhalational Anthrax Infection in the Mass Casualty Setting or for Postexposure Prophylaxis*

<table>
<thead>
<tr>
<th>Category</th>
<th>Initial Oral Therapy††</th>
<th>Alternative Therapy if Strain Is Proved Susceptible</th>
<th>Duration After Exposure, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Ciprofloxacin, 500 mg orally every 12 h</td>
<td>Doxycycline, 100 mg orally every 12 h; Amoxicillin, 500 mg orally every 8 h‡‡</td>
<td>80</td>
</tr>
<tr>
<td>Children</td>
<td>Ciprofloxacin, 20-30 mg/kg per day orally taken in 2 daily doses, not to exceed 1 g/d‡‡</td>
<td>Weight: 20 kg; amoxicillin, 500 mg orally every 8 h‡‡</td>
<td>80</td>
</tr>
<tr>
<td>Pregnant women‡‡</td>
<td>Ciprofloxacin, 500 mg orally every 12 h</td>
<td>Amoxicillin, 500 mg orally every 8 h‡‡</td>
<td>80</td>
</tr>
</tbody>
</table>

*Same as for nonimmunocompromised adults and children

†These recommendations are based on animal studies or in vitro studies and are not approved by the US Food and Drug Administration. (In vitro studies suggest ciprofloxacin 400 mg orally every 12 hours, or levofloxacin, 500 mg orally every 24 hours could be substituted for ciprofloxacin. (In vitro studies suggest that 100 mg of tetracycline orally every 6 hours could be substituted for doxycycline. In addition, 400 mg of gentamicin or minocycline, both fluoroquinolones with mechanisms of action consistent with ciprofloxacin, taken orally daily could be substituted.

‡‡According to the Centers for Disease Control and Prevention recommendations, amoxicillin is suitable for postexposure prophylaxis only after 10 to 14 days of fluoroquinolones or doxycycline treatment and then only if there are contraindications to these 2 classes of medications (e.g., pregnancy, lactating mother, age <18 years, or intolerance of other antibiotics).

††Doxycycline may also be used if antibiotic susceptibility testing, exhaustion of drug supplies, adverse reactions preclude use of ciprofloxacin. For children heavier than 45 kg, adult dosage should be used. For children lighter than 45 kg, 2.5 mg/kg of doxycycline orally every 12 hours should be used.


**Adapted from JAMA 2002; 287:2236-2252.**
The care of patients manifesting systemic effects of anthrax toxemia is considered strictly supportive since anti-toxins are unavailable. Clinical monitoring in an intensive care unit is appropriate. Fluid resuscitation and vasoconstrictors may be needed to maintain hemodynamic parameters in the normal range. Persons that develop respiratory distress or hypoxia may benefit from intubation and mechanical ventilation. If modern critical care measures are utilized, even persons presenting with inhalation anthrax may survive the illness.

**Prevention.** Bioport Corporation in Lansing, Michigan has the only license in the United States to produce the anthrax vaccine. It is an inactivated product that was first licensed in 1970 and is made from the cell-free filtrate of a nonencapsulated attenuated strain of *B. anthracis*. The vaccine induces antibody formation against protective antigen (anti-PA IgG) and appears to be very effective if given prior to exposure. The animal data regarding the vaccine’s efficacy in the post-exposure setting suggests that the vaccine by itself is not sufficient; however, three doses of the vaccine combined with appropriate antibiotic therapy may be efficacious in the post-exposure setting.

Prophylactically, the vaccine is given in a six-dose series (0, 2, and 4 weeks, and 6, 12, 18 months) and requires an annual booster. Preliminary data suggest that the first two doses may induce a sufficient antibody response to prevent inhalation anthrax following an aerosol exposure. Beginning in 1997, all
active and reserve military personnel in the United States were required to receive the anthrax vaccine. However, the vaccine is not available to the general public because supplies are limited and production remains modest.

Because of concern about adverse affects, the Institute of Medicine (IOM) published a report on the safety of the vaccine in 2002. The IOM concluded that the anthrax vaccine was effective against inhalation anthrax and that it was acceptably safe. The United States Army Medical Research Institute of Infectious Diseases (USAMRIID) has reported on its experience with over 1.6 million doses of the anthrax vaccine. Approximately 1% of inoculations were associated with a systemic adverse event. The most frequent systemic adverse event was headache (0.4% of doses). In contrast, injection site reactions were reported in 3.6% of doses. Importantly, the USAMRIID report noted no long-term sequelae to anthrax vaccine recipients.

Another issue is the use of antibiotics for post-exposure prophylaxis following exposure to spores of *B. anthracis*. Since there are no formal guidelines that cover all the possible scenarios, the Working Group on Civilian Biodefense recently recommended the same antibiotic regimen as would be used for treatment of mass casualties (See Table 4 above). Of note, prophylaxis should continue for a minimum of 60 days following exposure and persons taking prophylaxis should still be instructed to report any febrile or flu-like illnesses immediately.

**Regulations**

By Wisconsin law, anthrax in humans is considered a Category I Reportable Disease. Identification of a case or suspected case must be reported immediately to the patient's local health officer by phone, and in writing within 24 hours by submitting an Acute and Communicable Disease Case Report (DPH 4151).

Similarly, Wisconsin statues require that anthrax in animals be reported to the State Veterinarian within 24 hours of diagnosis.
Selected References


Definition of the Problem

Historically, brucellosis was one of the major zoonotic disease concerns in the United States. Veterinary control programs for brucellosis involving routine serologic testing, post-mortem assessment for pathologic lesions and, in the case of cattle, vaccination, have existed for many years. Because of these efforts, there are now only approximately 100 cases of human brucellosis diagnosed each year in the United States, and many of these are imported. Wisconsin’s livestock industry has been certified-free of bovine brucellosis since 1984, and cases of brucellosis in pigs have not been detected for many years. As such, the likelihood of encountering a naturally occurring case of locally acquired brucellosis in Wisconsin is remote. However, several issues warrant continuing to consider brucellosis as a possible diagnosis among rural residents. The first is that travel on agricultural study or consulting trips may allow for exposure in other parts of the world. In developing countries, several hundred thousand cases of brucellosis still occur in humans each year because of the continued presence of substantial animal reservoirs of the organisms. In proximity to the United States, bovine brucellosis remains one of the most serious animal diseases in Latin America, and swine brucellosis also remains endemic in that region. Second, a number of laboratory-associated infections have occurred and this mechanism of infection remains a concern. Third, the vaccines against brucellosis that are used in cattle in the United States utilize attenuated, live organisms that can pose a risk for human infection following accidental needle sticks. Finally, brucellosis has been considered as an agricultural and human bioterrorist agent.

The Etiologic Agents. Brucella spp. are small, aerobic Gram (-) coccobacilli. They are facultative intracellular organisms that can survive and multiply within phagocytic cells. Brucella culture requires a source of blood or serum in the media, and initial recovery from clinical samples may require prolonged (30+ days) incubation. Brucella are catalase (+), but oxidase, urease and hydrogen sulfide variable. Historically, multiple species of Brucella have been recognized and the individual species designations will be used here, although evidence suggests that these are all a single species with multiple serovars/biotypes. Each species of Brucella is typically associated with a particular species of animal. Specifically:

- **B. abortus** - cattle
- **B. melitensis** - goats and sheep
- **B. ovis** - sheep (primarily males)
- **B. suis** - pigs
- **B. canis** - dogs

Humans can be infected with all of these *Brucella* organisms except *B. ovis*, but the severity of human disease varies with the infecting strain. *B. melitensis* infection causes the most severe disease, followed in decreasing order of severity by *B. suis*, *B. abortus* and *B. canis*. The relative pathogenicity of *B. melitensis* and *B. suis* may be due to the fact that they are more resistant to bacteriolytic factors in serum than other *Brucella*. In addition, *B. melitensis* may also be more resistant to inactivation by gastric secretions.
Pathophysiology and Clinical Presentation

Pathogenesis. Historically, human infection by consumption of unpasteurized milk and contaminated-cheese was a serious problem. In regions of the developed world where pasteurization is practiced, such transmission is rare today. Instead, infection generally occurs by contamination of skin wounds or inoculation of the conjunctiva. The specific sources of the organism are placental tissues or vaginal secretions from infected animals, and to a lesser degree blood or urine from such animals. Contact with secretions from both domestic and exotic animals can pose risks, e.g., 5 zookeepers in Japan developed brucellosis in 2001 after attending the delivery of a baby moose, and disease in humans has been associated with contact with infected wild boar. Aerosols are also a potential source of infection for abattoir and research workers. Finally, as discussed above, needle sticks with bovine brucellosis vaccine can also be a route of infection for veterinarians or their staff.

Following initial infection, Brucella organisms spread through lymphatics and hematogenously to colonize reticuloendothelial cells in a variety of organs. Lipopolysaccharide is the organism’s major virulence factor. Control of the infection is dependent upon cell-mediated immune responses, but delayed-type hypersensitivity responses also contribute to the granulomas that typify brucellosis lesions.

Clinical Disease in Humans. After an incubation period of approximately 2-8 weeks (potentially shorter with needle stick exposures), patients develop flu-like symptoms of fever, chills and sweats, malaise, inappetence and head and body aches. (Interestingly, some patients report unusual taste sensations and malodous sweat.) This acute stage of disease can be followed by a prolonged waxing and waning series of recurrences of febrile episodes, hence the disease is commonly called “undulant fever.” (The disease is also called “Mediterranean fever” and “Malta fever” because of early work done on the disease in those areas of the world and the frequency of goat-associated brucellosis in those regions.)

Beyond this non-specific clinical presentation, organ-specific presentations may include: valvular endocarditis and arterial aneurysms; meningitis, encephalitis and other CNS manifestations (CSF cultures are positive in <50% of cases); arthritis, osteomyelitis, spondylitis, tenosynovitis, bursitis; hepatic and splenic granulomatous inflammation, and occasionally abscessation (especially with B. suis infections); ileocolitis with symptoms of nausea and diarrhea or constipation; orchitis; nephritis; and, abortion. Endocarditis is especially common with B. melitensis infections and is part of the reason for the increased severity of infection with this species of Brucella. The gastrointestinal and skeletal manifestations occur in 20-70% of patients, while the other complications are uncommon. Finally, needle stick infections with bovine B. abortus vaccines most commonly lead to a localized injection site reaction and fever and chills, but can also induce fulminant systemic infections.

Agricultural Factors

Brucella are fundamentally pathogens of animals, whereas human beings are accidental hosts. There is only limited evidence of person-to-person transmission of Brucella spp. Venereal transmission has been reported between a laboratory worker and his spouse, and B. melitensis abscesses in a woman’s breast
may serve as a source for infection for her infant.

As discussed previously, each species of *Brucella* is typically associated with a particular species of animals, although animals are sometimes cross-infected with *Brucella* when housed in proximity to other species (e.g., *B. suis* or *B. melitensis* in cattle maintained in contact with infected pigs or goats, respectively) or, in the case of carnivores, if they consume placental tissues from livestock. Clinically, infection with *B. abortus* in cattle occurs most commonly via ingestion, but it can also be acquired venereally. Adult cows are more susceptible than young stock. Bacteremia and colonization of the mammary gland and supramammary lymph nodes lead to suppurative placentitis and abortion. (Erythritol in the placenta may enhance the growth of *Brucella* spp.) This abortion form of bovine brucellosis has historically been known as “Bang’s disease” in honor of the Danish veterinarian who first associated *B. abortus* infection with abortion. Infection can also cause seminal vesiculitis and orchitis in bulls, and occasionally lameness and mastitis may occur as herd problems. Likewise, *B. melitensis* infections in sheep and goats cause late-term abortions or birth of weak lambs/kid goats, and *B. ovis* infection causes epididymitis in males. In pigs, *B. suis* infections are also associated with abortion and reproductive disorders in sows and orchitis in boars, but systemic spread of the bacteria commonly causes arthritis, spondylitis and abscesses. In dogs, *B. canis* infection can cause abortions at 40-60 days of gestation, epididymitis, orchitis and scrotal dermatitis in males, and diskospondylitis and uveitis following systemic spread in animals of either sex. (Cats, in contrast to dogs, are largely resistant to infection with *Brucella*.) Among non-domestic herbivores, bison, elk, reindeer and caribou can be infected with *Brucella* spp., but their role in transmission to livestock remains under debate. In this regard, controversy continues in the Greater Yellowstone Ecosystem regarding the role that bison and/or elk that wander outside the Park’s borders play in infecting domestic cattle, or vice versa. There is one suspected human case of brucellosis linked to the use of deer and elk urine as a scenting agent during hunting. Finally, brucellosis in horses presents slightly differently. There are no species of *Brucella* specifically adapted to horses, but infections with *B. abortus* and less commonly *B. suis* produce suppurative bursitis lesions called “fistulous withers” and “poll evil.”

**Management issues for human health**

**Diagnosis.** Because the symptoms of brucellosis are nonspecific, clinical diagnosis is fraught with difficulty. The correct diagnosis is much more likely to occur if a detailed history is obtained that includes occupation, contact with animals, travel, and ingestion of high risk foods (especially unpasteurized dairy products). Laboratory data is also nonspecific. The white blood cell count may be normal or low and the erythrocyte sedimentation rate is variable. Thus, the diagnosis requires direct or indirect evidence of the organism.

The diagnosis is confirmed when *Brucella* species are isolated from blood, bone marrow, or other tissues. Blood cultures are positive 15-70% of the time depending on the incubation period. Holding cultures for 4 weeks will increase the yield so microbiology personnel should be notified if brucellosis is in the differential diagnosis. In addition, the lysis concentration technique may shorten the incubation period. Cultures of bone marrow have been reported to produce a higher yield than blood cultures. A presumptive diagnosis may be made on the basis of morphology and culture properties, but confirmation typically requires oxidative metabolism or phage-typing techniques. Polymerase chain
reaction is promising but not yet considered definitive.

In the absence of positive cultures, serologic methods may be used to confirm the diagnosis of brucellosis. This requires high (i.e. more than 1:160) or rising titers of specific antibodies to *Brucella* species. Numerous techniques have been utilized to detect these antibodies. The Rose Bengal test is used as a rapid screening assay, but the results should be confirmed with the more reliable SAT method to detect *Brucella* specific antibodies. On rare occasions, the presence of blocking antibodies may result in a false negative assay. Therefore, negative or equivocal results obtained when there is high suspicion of the disease should be followed up by the use of the definitive *Brucella* enzyme linked immunosorbent assay. The historic “febrile agglutinin” test is considered nonspecific and should not be used to diagnose brucellosis.

**Treatment.** Antibiotics are effective in relieving symptoms, shortening the duration of illness, and reducing the number of complications due to brucellosis. Numerous medications appear to be effective against *Brucella* species in the laboratory. Unfortunately, *in vitro* susceptibility assays have proven to be unreliable in clinical practice. The intracellular location of the organism is probably responsible for the failure of β-lactam antibiotics. However, other drugs have proven benefit. The current recommendation to treat brucellosis is the combination of doxycycline (100 mg twice daily) together with streptomycin (1 g intramuscularly daily). The doxycycline is given for six weeks while the streptomycin is given for the first three weeks. An alternative regimen is the combination of doxycycline (100 mg twice daily) together with rifampin (600 mg daily) for a total of six weeks. The latter regimen is preferred for pregnant women.

Rarely, accidental needle stick inoculations with bovine brucellosis vaccines (strain 19) have led to human disease. Persons inadvertently exposed percutaneously to this vaccine should receive a three week course of prophylactic doxycycline and rifampin. The strain 19 vaccine is no longer commercially-available in the United States. Its replacement, the strain RB51 vaccine appears to be less virulent in humans than strain 19. Indeed, no human cases of brucellosis have been reported due to exposure to strain RB51. Nevertheless, prophylaxis following a percutaneous exposure with strain RB51 vaccine is considered prudent until further information becomes available. The prophylactic regimen consists of oral doxycycline 100 mg twice daily. Of note, rifampin is not needed in the latter regimen because strain RB51 is resistant to all rifamycins.

**Prevention.** Human brucellosis may be prevented by the control and elimination of disease in domestic animals. A cornerstone of this control historically was the widespread use of vaccinations among cattle in the United States. Vaccination of cattle is no longer mandatory in the U.S. because of the dramatic decrease in the prevalence of infection, but vaccine is still used widely in other parts of the world. Infection surveillance continues in the U.S. through serologic testing of cattle and post-mortem evaluation of all animals at slaughter for lesions suggestive of brucellosis.

Avoiding contact with animals, particularly placentas and vaginal secretions, helps to lessen the risk of human infection. The use of barriers such as protective clothing, gloves and protective eye wear should be promoted for veterinarians, farmers, and abattoir workers. The general public is protected by the widespread use of pasteurization. However, since this process is inconsistently used in the developing
world, persons traveling abroad should strictly avoid ingesting unpasteurized dairy products.

**Regulations**

By Wisconsin law, brucellosis in humans is considered a Category II Reportable Disease. Identification of a case or suspected case must be reported to the patient’s local health officer within 72 hours by submitting an Acute and Communicable Disease Case Report (DPH 4151) or by other means.

Similarly, Wisconsin statues require that brucellosis in cattle and swine must be reported to the State Veterinarian within 24 hours of diagnosis. Brucellosis in sheep and goats must be reported to the State Veterinarian within 10 days of diagnosis.
Selected References


Dermatophysitis and Dermatophilosis

Definition of the Problem

Dermatophytosis or “ringworm” is a common dermatologic problem in human medicine. While most cases are due to infection with the conventional “anthropophilic” dermatophyte fungi (those for which humans are the primary reservoir), humans can also be infected with “zoophilic” dermatophytes (those for which domestic or non-domestic animals are the primary reservoir) through contact with infected animals. Documentation of the source of infection in a patient can be important in identifying and/or preventing additional cases in family members or co-workers who may have been exposed to the same infected animals.

Dermatophilosis is always a zoonotic disease. The actinomycete etiologic agent is maintained on carrier animals, with release of zoospores into the environment when the infected skin becomes wet. This is a very rare infection in humans, with only 10 cases reported in the literature. Nonetheless, it should be considered as a differential diagnosis for exudative skin lesions in humans that have contact with animals.

The Etiologic Agents. Dermatophytes are fungi that predominantly cause superficial mycoses by invading and replicating in the stratum corneum of the skin and other keratinized tissues. The two primary genera of dermatophytes are *Microsporum* and *Trichophyton*. Zoophilic dermatophytes are associated with many species of domestic and non-domestic animals. Each individual dermatophyte may exhibit a wide host range or a very narrow host range. The most commonly encountered zoophilic dermatophytes in the United States and the most commonly implicated reservoir hosts for these fungi are as follows:

- *T. equinum* – horses
- *T. mentagrophytes-mentagrophytes* – horses, dogs, cats
- *T. verrucosum* – cattle
- *M. nanum* - pigs
- *M. canis* – dogs, cats

Among these, *M. canis* and *T. verrucosum* are the dermatophytes most commonly associated with human infections. Growth of these fungi in the laboratory requires special media such as Sabouraud’s dextrose agar with antimicrobials to inhibit growth of saprophytic bacteria or fungi. The arthroconidia and hyphae of dermatophytes can be identified in hairs and skin scrape materials from lesions after digestion in 10-20% KOH. The fungal elements can then be highlighted by staining with a solution of Evan’s blue and calcofluor white. In addition, it may be possible to identify *M. canis* by shining light from a Wood’s lamp on the area of the lesion or hairs and skin scrape materials removed from the lesions. However, both false-positive and false-negative fluorescence can be encountered, so this should not be relied on as a sole diagnostic procedure.

*Dermatophilus congolensis* is the causative agent of dermatophilosis. This is a filamentous actinomycete organism in which septa develop both horizontally and longitudinally, giving rise to rows
of coccoid cells that become the infectious zoospores. Like dermatophytes, this organism is largely restricted to replication in epidermal cells and keratinized structures. The characteristic appearance of filaments containing paired rows of cocci/zoospores can be identified in wet mounts from lesions by methylene blue staining and in dry mounts by Giemsa (preferable over Wright’s and Gram) staining. The organism can be cultivated in the laboratory on blood or brain-heart infusion agar.

**Pathophysiology and Clinical Presentation**

**Pathogenesis.** The infectious units of dermatophytes are the vegetative arthroconidia that form from fungal hyphae. These structures can survive for many months in the environment, so direct contact with an infected animal is not absolutely required. However, zoonotic infections often involve a documentable animal contact. Invasion of stratum corneum cells or hair shafts is followed by vegetative growth of the fungi. Individual differences in susceptibility to infection may involve differences in skin moisture, the fatty acid composition of the sebum and the presence of unsaturated transferrin in sweat that inhibits fungal growth. The lesions of zoophilic dermatophytes may be more inflamed than those of the anthropophilic fungi.

In dermatophilosis, the zoospores are attracted to CO₂ diffusing off the skin surface. They germinate on the skin surface and send hyphal elements into the epidermis. Branching hyphae then laterally invade the hair follicles. The body’s inflammatory responses include accumulation of neutrophils under the infected epidermis and serous exudation, but the epidermal basement membrane is thought to exclude the organism from deeper tissues. Eventually thick scabs of dried serum and sloughing epidermal cells and hairs form.

**Clinical Disease in Humans.** The lesions of ringworm/dermatophytosis in humans in their most classical form are round-shaped patches of scaly skin with slightly raised, reddened annular margins (the “tinea circinata” lesion). However, the range of lesions extends to large suppurative kerions. The location of the lesions is often characteristic for the anthropophilic dermatophytes (e.g., tinea capitis on the head), but varies for the zoophilic dermatophytes and depends on the site of animal or fomite contact. In immunocompromised patients, particularly those with compromise of their cellular immune responses, deep mycotic infections that extend beyond the keratinized skin surface can occur. These can present as subcutaneous granulomas and draining tracts, sometimes with mycetoma-like grains. More rarely, fatal infections of internal organs (liver, brain) can occur in these patients.

Dermatophilosis in humans appears to be exceedingly rare. The presentation is one of a dermatitis with multiple 2-5mm white pustules that neither spread nor coalesce. Resolution occurs in several weeks.

**Agricultural Factors**

Dermatophytosis can occur through contact with many domestic animals, but dogs, cats, cattle and horses generally pose the greatest risks. Infections occur most commonly in the young of each species or in animals with underlying health problems. It is particularly important to recognize that cats may sometimes serve as subclinical carriers of zoonotic dermatophytes. The risk of infection from cats is greatest from kittens, and especially those from shelters or catteries with a history of dermatophytosis.
The lesions of dermatophytosis in animals vary greatly. The typical circular reddened lesion seen in humans is relatively uncommon. Dermatophyte infections in animals target hair follicles and more typically present as focal or multifocal areas of alopecia with associated papules and hyperkeratosis. The hyperkeratosis can create lesions that appear as greyish-colored, raised, crusted plaques. Dermatophytosis can also present as a more diffuse folliculitis/dermatitis, as nodular kerions or as a pustular condition because of opportunistic secondary bacterial infection.

Dermatophyllosis most commonly occurs in sheep, goats, cattle and horses, although dogs and cats are sometimes affected. Dermatophyllosis occurs predominantly during wet times of the year since moisture enhances the release of the zoospores. In addition, nutritional deficiencies may predispose animals to clinical disease. The lesions of dermatophyllosis are often described as “paint-brush”-like because the surface exudates glue adjacent hairs together so as to resemble a fine paint brush. If these crusts are removed, the underlying skin surface can be seen to be ulcerated and erythematous. Dermatophyllosis in animals goes by a variety of names. “Strawberry foot rot” reflects involvement of the skin above the hoof or between the claws of the hoof and the appearance of the ulcerated granulomatous skin lesions beneath the scabs. Dermatophyllosis is also called “lumpy wool disease” and “streptothricosis.” Streptothricosis should not to be confused with “sporotrichosis” caused by infection with Sporothrix schenkii. (The later organism is also zoonotic. Infections in both animals and humans typically occur because of contamination of skin wounds with this dimorphic fungus in soils, but infected cats pose a risk for direct infection of humans even in the absence of a pre-existing wound.)

Control of dermatophyllosis in animals is based on management factors to maintain a clean, dry environment. A clean environment is also important to the control of dermatophytosis in animals, as well as prompt recognition of infected animals and then prevention of animal-to-animal transmission. Recently, dermatophyte vaccines have become available for animals. In particular, an inactivated *M. canis* vaccine is commercially-available for cats. This vaccine has been shown to induce serum antibodies against *M. canis* and to reduce the severity of clinical lesions following challenge infection, but it does not prevent infection. As such, it is of minimal value in limiting zoonotic transmission of *M. canis* from cats. A live strain of *T. verrucosum* (LFT-130) has been employed for many years as a vaccine in cattle in Eastern Europe and Scandinavia. This vaccine has been effective in reducing the prevalence of *T. verrucosum* infection in cattle and, thereby, among in-contact human beings. However, it is not commercially-available in the United States.

**Management Issues for Human Health**

**Diagnosis.** Humans are less commonly affected by zoophilic dermatophytes than the anthropophilic organisms. However, human hosts that come into contact with an animal colonized with a zoophilic dermatophyte may develop a significant inflammatory response because of an allergic hypersensitivity reaction. Anthropophilic dermatophytes, in contrast, do not typically provoke such an intense inflammatory response. In addition, the location of the reaction is typically related to areas of the skin that come into direct contact with animals.

The first step in the diagnosis is to obtain a skin scraping, hair clipping or nail clipping. The tissue should be divided in half so that both fungal cultures and microscopy may be done. Prior to
microscopic examination, the clinical specimen should be soaked in 10-20% KOH. Examination will reveal fungal elements. However, since most practitioners are not familiar with zoophilic dermatophytes, culture is considered more definitive. Nevertheless, there is a 50% false negative rate for fungal cultures so repeat samples may be necessary.

**Treatment.** The treatment of zoophilic dermatophytes is similar to anthropophilic dermatophytes except that steroids may be needed if there is a significant inflammatory response. If possible, mild cases should be treated with topical therapy. A keratinolytic such as Whitfield's ointment (salicylic and benzoic acid compound) may be of benefit. However, specific antifungal therapy is typically more effective. A number of compounds are now available for human use. These include tolfanate, clotrimazole, ketoconazole, miconazole, sulconazole, oxiconazole, naftifine, terbinafine and cyclopirox olamine. Many of these are available as over-the-counter creams, lotions, and powders. Systemic treatment with oral antifungal medications (terbinafine or itraconazole) may be indicated if the infection involves deep tissues or the scalp. A typical course of terbinafine is 250 mg per day for 2-4 weeks. Alternatively, itraconazole 200 mg per day for 2-4 weeks is also effective. Of note, itraconazole solution is preferred over itraconazole tablets because the latter formulation is poorly absorbed through the human digestive tract.

**Prevention.** The primary way to prevent zoophilic dermatophytosis is to avoid direct skin contact with animals colonized or infected with these fungi. Because animal dermatophyte infections may be subclinical, avoiding this contact is difficult at best.

**Regulations**

Dermatophytosis is not a reportable disease in either humans or animals. However, by Wisconsin statues, dermatophilosis in animals must be reported to the State Veterinarian within 10 days of diagnosis.
Selected References


Erysipelothrix Rhusiopathiae Infection

Definition of the Problem

Infection with *Erysipelothrix rhusiopathiae* is an occupational disease of primarily veterinarians, abattoir workers and farmers exposed to infected animals. The most important animal source is pigs. However, a wide variety of other animals can be infected, including fish and other aquatic animals. In fish, the organism is carried subclinically in the mucoid slime covering the scales. Infection of humans from fish exposure is referred to as “fish handler’s disease.” Finally, infection of humans does not require direct contact with infected animals. *Erysipelothrix rhusiopathiae* can also be acquired indirectly through contact with contaminated soil, in which the bacteria remain infectious for weeks to months.

The cutaneous form of human infection is called “erysipeloid.” This term and the disease it refers to should be distinguished from “erysipelas,” a cellulitis in humans caused by infection with hemolytic *Streptococcus* spp. Unfortunately, infection of animals with *Erysipelothrix rhusiopathiae* is also referred to as “erysipelas.”

The etiologic agent, *Erysipelothrix rhusiopathiae* is a thin, pleomorphic, weakly-staining Gram (+), facultatively anaerobic organism. It may be alpha-hemolytic on blood agar, is catalase, oxidase, indole, Voges-Proskauer and methyl red negative, hydrogen sulfide positive, and ferments glucose, fructose, lactose and galactose without gas formation. At least 22 serotypes have been described.

Pathophysiology and Clinical Presentation

Pathogenesis. Infection with *Erysipelothrix rhusiopathiae* occurs primarily through breaks in the skin (most commonly on the hands), although there are reports of septicemic *Erysipelothrix* infection and endocarditis in humans who ate undercooked pork or smoked fish products. The bacteria produce two enzymes that are thought to be virulence factors, neuraminidase and hyaluronidase. The lesions of erysipeloid are the result of thrombotic vasculitis.

Clinical Presentations in Humans. The most common presentation of *E. rhusiopathiae* infection is the erysipeloid cutaneous condition that develops 1-7 days after contamination of a skin wound. This is characterized by a unique, raised, cellulitis lesion that is highly pruritic (intense burning sensation) and accompanied by purplish-red discoloration and edema of the skin. As the lesions spreads, the central portion may blanch, and vesicles may form. Fever and regional lymphadenopathy occur along with the skin lesion in less than one-third of cases of uncomplicated erysipeloid. This condition differs from streptococcal and staphylococcal cellulitis by the lack of suppuration and the presence of intense pain and purplish-red discoloration.

Complications of this localized cutaneous form of infection include a more diffuse form of cellulitis extending proximal to the initial site of infection, arthritis of the underlying joints, and bacteremia and systemic spread. Valvular endocarditis is the most common result of bacteremia. In one study, only 36% of endocarditis patients had evidence of pre-existing cutaneous erysipeloid. Finally, brain
abscesses, osteomyelitis and chronic arthritis in the absence of endocarditis have also been reported with *E. rhusiopathiae* bacteremia.

**Agricultural Factors**

*Erysipelothrix rhusiopathiae* is subclinically carried in the pharynx and shed in the feces, urine and oronasal secretions of up to 30% of pigs. It can also be isolated from feces, soil and water in an infected animal’s environment. In one study conducted in the United States, the organism could be isolated from the soil in 25.6% of swine enclosures tested. With the progressive move towards confinement housing of pigs, long-term soil contamination becomes less of a concern, but the organism may still be present in even small quantities of feces on the floors of indoor swine housing facilities.

Beyond serving as subclinical sources of infection for humans, pigs also develop *E. rhusiopathiae* -induced disease. As in humans, infection in pigs ranges in severity from a cutaneous condition referred to as “diamond skin disease” (diamond-shaped lesions reddish-purple or more diffuse edema and erythema) to bacteremia with fever, prostration, anorexia, vomiting and reluctance to walk. The case fatality rate in this acute systemic form of disease in very high. Finally, pigs can also develop chronic endocarditis and arthritis following *E. rhusiopathiae* infection. Pigs are routinely vaccinated against *E. rhusiopathiae* in the United States and other parts of the world, although as the prevalence of disease decreases, vaccination coverage also tends to decrease. This may lead to local outbreaks of disease in naïve populations. In 2001, 190 pigs at a county fair in Iowa were shipped to slaughter because of exposure to pigs with erysipelas.

Other domestic animals of concern for *E. rhusiopathiae* infection include turkeys and other fowl species (chickens, chukars, ducks, emus, parrots, peacocks, pheasants), lambs and calves. Infection in turkeys causes a bacteremia associated with profound weakness, and cyanosis, erythema and hemorrhage of the comb and snood. This condition is commonly referred to as “blue comb.” Infections in lambs and calves typically occur through the umbilicus in the immediate post-partum period and result in polyarthritis.

**Management Issues for Human Health**

**Diagnosis.** The diagnosis should be considered in a patient with erysipeloid, a subacute cellulitis that most typically involves the fingers. However, the definitive diagnosis is obtained when the organism is isolated from a biopsy specimen or blood. Clinicians taking care of patients that present with cellulitis involving the hands or fingers should inquire about contact with pigs and fish. If blood cultures are negative, an aspirate of the center or leading edge of the cellulitis should be obtained in an attempt to isolate the organism. There are no reliable serologic tests for the diagnosis of infection in humans.

**Treatment.** Cutaneous infection in humans resolves spontaneously 3-4 weeks after its onset. However, antibiotic therapy will hasten its resolution. Penicillin is the drug of choice although cephalosporins may also be utilized. Curiously, the organism is resistant to vancomycin. This is important because vancomycin is often used to treat skin and soft tissue infections out of concern for methicillin-resistant...
*Staphylococcus aureus.* Infection with *E. rhusiopathiae* should be considered when a person with cellulitis does not respond to vancomycin. Invasive disease including bacteremia and endocarditis requires systemic therapy with intravenous penicillin (20 million units per day) for 4-6 weeks, whereas milder forms of illness can often be treated with oral medications. Ciprofloxacin can be used as an alternative if a patient is allergic to penicillin.

**Prevention.** Infection may be prevented in humans by avoiding direct contact with animal body tissues, animal secretions/excretions and contaminated soils. Protective barriers such as gloves will help to prevent infection in persons with high-risk occupations such as veterinarians. Control of the organism in swine is due to improved waste disposal and the use of vaccines available for veterinary practice.

**Regulations**

*Erysipelothrix rhusiopathiae* infection is not a reportable disease in Wisconsin in either humans or animals.
Selected References


Hepatitis E Virus - a Zoonosis?

**Definition of the Problem**

Hepatitis E is now recognized as the major form of “non-A, non-B enterically-acquired hepatitis” in humans. Hepatitis E has occurred in large-scale outbreaks among young adults in many parts of the world (Asia, Africa, Mexico), but no outbreaks have been reported in the United States, only sporadic individual cases. Nonetheless, antibodies to the etiologic agent, hepatitis E virus (HEV), may be found in apparently healthy individuals in non-endemic countries. The virus is transmitted via the fecal-oral route and minimal person-to-person transmission occurs.

**The Etiologic Agent.** Hepatitis E virus is an unclassified virus, thought initially to be a calicivirus. It is a nonenveloped, (+) sense RNA virus.

**Pathophysiology and Clinical Presentation**

**Pathogenesis.** Hepatitis E virus is shed in the feces of infected people and is most prevalent in under-developed regions of Mexico, Africa, India and Asia with poor sanitation conditions. Hepatitis E virus is spread in epidemic situations primarily via contaminated water sources, and outbreaks are often associated with periods of heavy rainfall that enhance fecal contamination of water reservoirs. Many aspects of the pathogenesis are unclear, including whether viral replication occurs in the gastrointestinal tract prior to spread to the liver. Pathologic lesions may include focal hepatocellular necrosis, pseudoglandular hepatocyte architecture and intrahepatic cholestasis, and the hepatic damage and inflammation may be immune-mediated.

**Clinical Disease in Humans.** Symptoms such as anorexia, nausea, vomiting, abdominal pain and jaundice develop after a 4-8 week incubation period. The overall clinical picture is similar to that with hepatitis A. Progression to fulminant hepatitis and liver failure occurs rarely, and the overall case fatality rate is 1-2%. However, case fatality rates following HEV infection are much higher among pregnant woman (approaching 20%) than in the general population. The infection is most severe when contracted during the third trimester. The specific reason(s) for this pattern of enhanced disease during pregnancy are not known. Unlike hepatitis B and hepatitis C, neither chronic liver disease nor hepatocellular carcinoma are associated with infection with hepatitis E virus.

**Agricultural Factors**

An interesting development in the past several years is the possibility that some cases of HEV infection may represent zoonoses. The rate of seropositivity in non-endemic countries was initially found to be ~1-2%, but in a recent study, 17-18% of blood donor samples tested from 8 states in the United States were positive for anti-HEV antibodies. In the same study, 23-26% of swine veterinarians were seropositive, although the significance of this finding is unclear since there was no statistical correlation to needle-sticks injuries or measures of contact with pigs. However, another recent study (Favorov, M. and C.W. Olsen, unpublished results) found a higher rate of seropositivity among swine farmers in Wisconsin, compared to an age- and
sex-matched controls from urban Milwaukee, WI. The reservoir of HEV has been assumed to be humans themselves. However, several recent findings suggest that pigs may play a role:

- A HEV-like virus (swine HEV [swHEV]) was isolated from pigs in the United States in 1997.

Serologic testing indicates that this virus is widespread in pigs:

- >80% seropositivity by 4-5 months of age among pigs in the United States
- 38-56% seropositivity among pigs in Canada
- 37% seropositivity among pigs in Taiwan
- 30% seropositivity among pigs in Australia
- Though clinically normal, infected pigs have histologic evidence of hepatitis, including multifocal lymphoplasmacytic infiltrates and focal hepatocellular necrosis. In addition, the virus may also replicate in lymph nodes and the colon in pigs.
- Sequence analysis of swHEV indicates that it is highly homologous to, but distinct from, most strains of human HEV. However, swHEV-like viruses (US1 and US2 strains with 94-98% sequence homology to swHEV itself) have been isolated from 2 people in the United States.
- Swine HEV has been shown to infect non-human primates and the human US1 and US2 strains have also been shown to infect pigs.
- Similar pairs of closely related human and swine isolates have been reported in Taiwan, China and The Netherlands.

Despite this information, it remains unclear whether exposure to swHEV in people can explain the occurrence of seropositivity to human HEV among people in non-endemic regions of the world, including the United States. In addition, exposure to other animals may play a role, since anti-HEV antibodies have also been detected in rodents, chickens, dogs, cows, sheep and goats.

**Management Issues for Human Health**

**Diagnosis.** The diagnosis of hepatitis E infection in humans is made using serologic methods. Persons presenting with acute hepatitis should be suspected of having HEV infection if they have recently traveled to a developing country or if they have come into contact with pigs. There are commercial tests for HEV-specific IgM and IgG available in Asia, Europe and Canada, but not in the United States. However, numerous research laboratories and reference laboratories have the capacity to test clinical specimens. If a serum sample is obtained from 1-4 weeks after the onset of symptoms, IgM anti-HEV can be detected in 96% of persons. Since 50% of persons will have undetectable levels of IgM anti-HEV three months after presentation, the diagnosis of acute hepatitis E infection may be made if either IgM anti-HEV is found or a very high titer of IgG anti-HEV is detected.

**Treatment.** There is no specific antiviral therapy for HEV infection. Persons with HEV infection should be treated symptomatically and every effort should be made to minimize drugs and products that may be harmful to the liver, including alcohol.

**Prevention.** Persons traveling to HEV-endemic areas should avoid drinking water (as well as beverages
with ice) of unknown purity. They should also avoid uncooked/undercooked shellfish as well as
uncooked fruits and vegetables not peeled or prepared by the traveler. Immune serum globulin (ISG)
produced from pools of serum obtained from blood donors in Western countries has failed to prevent
HEV infection. Currently, no vaccine is available for human use. Similarly, no antiviral medications are
known to be effective for post-exposure prophylaxis. If this disease is indeed a zoonoses, then washing
hands after direct contact with swine or their waste should help to decrease transmission to persons.
Similarly, hand washing practices should be encouraged in all persons, not just persons with acute HEV
infection and food handlers.

Regulations

By Wisconsin law, hepatitis E in humans is considered a Category II Reportable Disease. Identification
of a case or suspected case must be reported to the patient’s local health officer within 72 hours by
submitting an Acute and Communicable Disease Case Report (DPH 4151) or by other means.
Hepatitis E is not a reportable disease in animals.
Selected References


Definition of the Problem

Leptospirosis is a classic zoonosis. It exists throughout the world, but is most common in tropical regions where frequent rain storms and the lack of freeze-thaw cycles enhance contamination of and persistence of the *Leptospira* organisms in lakes and streams. Human-to-human transmission of *Leptospira* is very rare. Instead, human infections are virtually always associated with direct contact with infected domestic or wild animals, or indirect contact via contaminated water. This epidemiological pattern is reflected in some of the colloquial names for human leptospirosis: “swine herder’s disease,” “rice-field fever,” and “cane-cutters fever.” Veterinarians, farmers and abattoir workers are specifically at increased risk for leptospirosis. In 1998, 9 people who worked with the University of Missouri swine herd developed leptospirosis. The major risk factors for these patients, above and beyond contact with the pigs, were smoking and drinking beverages while working with the pigs. Because of the ability of *Leptospira* to produce persistent infections in the renal tubules, with prolonged shedding of the organism in urine, veterinarians are cautioned to handle even routine urinalysis specimens as if they contain leptospires, taking precautions such as gloves and a face shield (to prevent mucosal splashes). Similarly, farmers are at risk from urine splashes from animals and possibly even just aerosolization of urine in a confined animal housing setting. Because of the prolonged survival of *Leptospira* in water, other occupations at risk include sewer workers, members of the military, and rice and sugar cane plantation employees. Finally, concern is growing for the risk of acquiring *Leptospira* from contaminated water by kayakers, triathletes and other recreationalists.

The Etiologic Agent. *Leptospira* are tightly-coiled spirochetes with bent or hooked ends. There are over 200 serovars of pathogenic *Leptospira*, but they are now all considered as one species, *L. interrogans*. These are distinct from the saprophytic, environmental, non-pathogenic *L. biflexa*. Culture of *Leptospira* requires special media such as Fletcher’s, EMJH or Tween 80-albumin, and prolonged incubation (5+ weeks) at 28-30°C.

Pathophysiology and Clinical Presentation

Pathogenesis. It is likely that any of the serovars of *L. interrogans* can be pathogenic in humans, but certain serovars are implicated in human disease more commonly than others. These include: *L. canicola*, *L. icterohaemorrhagiae*, *L. pomona*, *L. autumnalis*, *L. grippotyphosa*, *L. hebdomidis*, *L. ballum* and *L. australis*. Following penetration of mucosal surfaces (or less commonly entrance through cutaneous wounds), *Leptospira* spreads hematogenously to virtually all organs in the body. However, infections of the liver, kidneys and CNS are of most importance clinically.

Clinical Disease in Humans. Human infections with *Leptospira* are broadly classed as icteric (10% of cases) or anicteric (less severe; 90% of cases).

“Weil’s disease” (most commonly due to infection with *L. icterohaemorrhagiae*) is the name for the icteric form of leptospirosis with involvement of the liver and kidneys. After an incubation period of 7-12 days, patients develop fever (biphasic), headache and flu-like illness. This is followed within a few
days by hepatomegaly, jaundice and potentially renal insufficiency, hemorrhage and hypotensive shock. Infection of the liver appears to induce primarily functional hepatocellular damage rather than frank necrosis. ALT and AST levels rarely exceed 100-200 and SAP levels are generally only moderately elevated. Similarly, renal tubular damage and compromise of renal function may be due to hypoxemia, hypotension or a toxic factor rather than fulminant structural damage. Urinalysis may demonstrate proteinuria, hematuria and tubular casts. Coagulation abnormalities may develop because of reductions in the production of clotting factors by the liver, the widespread vasculitis that typifies leptospirosis, or consumption of clotting factors secondary to LPS-induced stimulation of platelet activation. Recovery can take months and the case fatality rate can approach 5-10%.

The less severe, anicteric form of leptospirosis presents again as an initial flu-like illness, but this can be followed by a second phase of intense headaches, severe myalgia, abdominal pain and nausea, and sometimes rash, conjunctivitis and conjunctival hemorrhage. The most important potential sequelae is meningitis. The meningitis appears to be immune-mediated and the organism is generally not present in the CSF by the time clinical signs develop.

A relatively recently described clinical presentation of leptospirosis affected about 2,500 people and killed at least 16 individuals in Nicaragua in 1995. This outbreak of what was called “Mystery disease” occurred following a period of substantial flooding. Flooding increases the potential for waterborne exposure and may drive infected rats into human dwellings. Specific risk factors for infection in this outbreak included walking in creeks, having household rodents, and owning dogs with Leptospira serum antibody titers >400. The unique clinical feature of some of these cases was pulmonary hemorrhage. This rare manifestation of leptospirosis was previously documented only rarely in Brazil, Korea and China. Similar manifestations have been identified more recently in a visitor returning from Africa.

**Agricultural Factors**

Specific serovars of *L. interrogans* are “hosted-adapted” to particular reservoir species and generally do not cause disease in those hosts. These include:

- *L. canicola* in dogs
- *L. icterohaemorrhagiae* in rats
- *L. grippotyphosa* in voles, raccoons and other small mammals
- *L. bratislava* in pigs and rats and other small mammals

Rats are the most common source of infection for human beings worldwide. In the United States, however, the most common sources of infection for humans are dogs and livestock species (especially cattle and pigs - infections occur, but are much less common in sheep and goats), followed in decreasing order of frequency by rodents and other wild mammals. Infection is very rare in cats. Human infections can occur through direct contact with infected animals (especially their urine), but more commonly occur indirectly by exposure to the organism in the environment (especially in standing water) while working or recreating outdoors.
In cattle and pigs, *Leptospira* infections are manifest clinically by abortion and other reproductive disorders. (Systemic disease with fever, icterus and hemoglobinuria occur very rarely.) In dogs, many, if not most, *Leptospira* infections are subclinical. Historically, clinical infections in dogs presented most commonly as fever, anorexia and vomiting that progressed to signs of hepatic disease and petechial and ecchymotic hemorrhages. This acute form of hepatic and hemorrhagic disease is similar to Weil’s disease in human beings and is most often associated with infection with *L. icterohaemorrhagiae*. Over the past few decades, however, this form of infection has been greatly diminished by widespread vaccination. Yet the overall prevalence of leptospirosis in dogs in the United States and Canada has increased since 1983, according to a large study of nearly 2 million canine patients examined at Veterinary Medical Teaching Hospitals. Along with this trend, a novel form of leptospirosis, presenting as acute renal failure (ARF) with fever, anorexia, lethargy, depression, vomiting, polyuria and polydipsia and sometimes abdominal pain has been identified in dogs in WI, MI, NY, NJ and GA. This syndrome, occurring most commonly in the fall of the year, has been associated primarily with *L. grippotyphosa, bratislava* and/or *pomona* (i.e., not the “typical” canine leptospires *L. icterohaemorrhagiae* and *L. canicola*) and is characterized by unique ultrasonography and histopathology findings. Interestingly, ARF in a person has also been linked recently to *L. grippotyphosa* infection. Finally, *Leptospira* infection occurs in horses, most commonly presenting as a persistent or recurring uveitis. This condition has traditionally been thought to be immune-mediated, but recent evidence suggests persistent active infection may also play a role.

Vaccination against leptospirosis is widely practiced for dogs, cattle and pigs in the United States. However, it is very important to realize that vaccinated animals, though possibly protected from clinical disease, can still persistently shed *Leptospira* organisms in their urine and, therefore, serve as a source for infection of human beings.

**Management Issues for Human Health**

**Diagnosis.** The diagnosis of leptospirosis is confirmed by isolating the organism in urine, blood or cerebrospinal fluid. Unfortunately, isolation of the *L. interrogans* is extremely difficult. Even in experienced hands, the yield is considered very low and the cultures may take up to 16 weeks to turn positive. Darkfield examination is also fraught with difficulty and has been associated with both false positives and false negatives. Polymerase chain reaction is promising but not widely available to date.

In contrast to direct identification, serologic methods are the most reliable method of confirming the diagnosis of human leptospirosis. Paired serum samples should be collected: the acute specimen collected 1-2 weeks after symptom onset and the convalescent specimen collected 3-4 weeks after symptom onset. The microhemagglutination test (MAT) done at the CDC reference laboratory uses live organisms and is considered to be the standard serologic test for the detection of specific leptospiral antibodies. Although it is time consuming to perform and is considered hazardous work, it is both highly sensitive and specific. A titer of at least 1:800 in the presence of compatible symptoms is considered to be strong evidence of a recent or current infection. Suggestive evidence of a recent or current infection includes the presence of compatible symptoms combined with either a single titer of at least 1:200 or a titer of at least 1:100 on consecutive specimens. Newer methods under investigation include a specific IgM enzyme linked immunosorbent assay (ELISA) as well as an indirect hemagglutinin assay (IHA).
Treatment. Supportive therapy and close observation are essential for detecting and treating dehydration, renal failure, and hypotension in leptospirosis. Initial clinical trials failed to show the benefit of treating leptospirosis. More recently, however, placebo-controlled clinical trials have demonstrated the efficacy of penicillin therapy in both severe and late leptospirosis. Also, oral doxycycline begun within 3 days of symptom onset has been shown to reduce the severity and duration of illness. Therefore, the current recommendations for treatment are as follows:

For mild disease:  
Doxycycline 100 mg po bid for 7 days, or  
Amoxicillin 500 mg po qid for 7 days, or  
Ampicillin 750 mg po qid for 7 days

For moderate-to-severe disease:  
Penicillin G 1.5 million units IV q 6 hours, or  
Ampicillin 0.5-1.0 g IV q 6 hours

Intravenous penicillin has been shown to decrease the duration of laboratory abnormalities as well as constitutional symptoms even in patients with advanced disease. Similar to syphilis, the treatment of leptospirosis may produce a Jarisch-Herxheimer reaction. This reaction manifests as a paradoxical worsening of clinical signs and symptoms as the spirochetes die soon after they come into contact with the first dose of antibiotics. Therefore, patients receiving intravenous penicillin should be monitored for hypotension and other shock-like signs.

Prevention. As mentioned above, persistent shedding of *Leptospira* in the urine of infected animals occurs commonly. Thus, veterinarians are cautioned to handle all urine specimens as if they contain leptospires, taking precautions such as gloves and a face shield (to prevent mucosal splashes). Similarly, farmers are at risk from urine splashes from animals and possibly even just aerosolization of urine in a confined animal housing setting. Similarly, the organism may survive for prolonged periods in water. Thus, sewer workers, members of the military, and rice and sugar cane plantation employees are at risk of acquiring this infection. Lastly, participation in recreational activities by kayakers and triathletes has raised concern. Therefore, avoiding direct contact with infected animals and indirect contact with water and soil contaminated with animal urine is the cornerstone of preventing human leptospirosis. Keeping a high standard of hygiene in abattoirs and farms should also be encouraged. The use of protective clothing such as rubber gloves and high rubber boots for persons in high-risk occupations is warranted. Kayak drills that involve capsizing should be done in swimming pools and swimming in fresh water ponds should be avoided. Decontamination of large bodies of fresh water is impractical; however, rodent pest control has been shown to be effective in certain settings.

A field study in Panama demonstrated that chemoprophylaxis with oral doxycycline 200 mg once per week has an efficacy of 95% in preventing leptospirosis in military personnel. Failure of post-exposure prophylaxis with penicillin has been reported. Therefore, oral doxycycline (100 mg po bid for 7 days) is the preferred agent for preventing human leptospirosis following exposure to the causative agent.
Regulations

By Wisconsin law, leptospirosis in humans is considered a Category II Reportable Disease. Identification of a case or suspected case must be reported to the patient’s local health officer within 72 hours by submitting an Acute and Communicable Disease Case Report (DPH 4151) or by other means.

Wisconsin statutes also require that leptospirosis in animals must be reported to the State Veterinarian within 10 days of diagnosis.
Selected References


Listeriosis is a potential zoonotic disease for those in contact with infected animals or environments contaminated by infected animals. It is a disease of particular concern for pregnant women and their fetuses/neonates, the elderly and the immunosuppressed. Beyond zoonotic transmission, listeriosis has emerged recently as an important foodborne disease. *Listeria monocytogenes* is somewhat unique in that it is both heat and cold tolerant. As such, it can survive pasteurization if bacterial counts in the milk are >1,000 bacteria/ml and, conversely, it can grow at refrigerator temperatures in contaminated products. Foodborne infection has been documented in association with soft cheeses, coleslaw, fresh vegetables, meats and milk. Examples of recent foodborne incidents include:

- In 1994, 45 persons attending a picnic in Illinois developed listeriosis after consuming chocolate milk thought to have been contaminated after pasteurization.
- In 1998-99, at least 50 people across 11 states were sickened after consuming contaminated hot dogs.
- In March 2000, *Listeria* bacteria were detected in pre-prepared cheeseburgers sold to convenience stores and vending machines, and in cold smoked fish products in the United States.
- From May-November 2000, 29 people across 10 states in the United States were sickened by eating contaminated deli turkey.
- Nearly 200 tons of luncheon meats were recalled in the United States in November 2001 because of *Listeria* contamination.

Despite the recent focus on foodborne listeriosis, however, this disease should remain a concern for people involved in agricultural activities.

**The Etiologic Agent.** *Listeria monocytogenes* is an aerobic, non-spore forming, Gram (+), bacillus. It is a facultative intracellular organism that is able to escape from phagolysosomes (listeriolysin O toxin disrupts the phagolysosome membrane) and replicate in the cytoplasm of phagocytic cells. Culture recovery of the organism is optimized by use of a Todd-Hewitt broth-based enrichment media with antibiotics to inhibit the growth of other bacteria. There are at least 11 serotypes of *L. monocytogenes*, with types Ia, Ib and IVb being the most commonly implicated in human clinical disease (98% of cases).

**Pathophysiology and Clinical Presentation**

**Pathogenesis.** Infection occurs most commonly following ingestion of the organism, but may also be able to occur through skin or conjunctival breaks. After crossing the epithelial cell carrier, hematogenous dissemination throughout the body can occur. The listeriolysin O toxin is a critical virulence factor, and iron substantially enhances growth of *L. monocytogenes* (thus clinical associations with hemochromatosis and dialysis). Resistance to *L. monocytogenes* is mediated primarily by cell-mediated immune responses. As such, *L. monocytogenes* infections are of particular significance in patients with compromise of their cellular immune functions, e.g. those with neoplastic disease, AIDS,
high-dose corticosteroid therapy patients, the elderly and pregnant woman. Specifically, the incidence of listeriosis in AIDS patients has been estimated to be 65-300 times the rate in age-matched controls from the general public. Likewise, it has been estimated that pregnant woman account for 27% of all cases of listeriosis and 60% of cases in people 10-40 years of age.

**Clinical Disease in Humans.** Infection may lead to a limited gastroenteritis, or systemic spread and sepsis affecting a variety of organs, but especially the central nervous system and the conceptus.

**Gastroenteritis.** Gastroenteritis develops most commonly following foodborne exposure. It may be the only clinical manifestation of infection or it may occur antecedent to systemic infection. After an incubation period of approximately 10-36 hours, clinical symptoms most commonly include fever, chills, headache, malaise, and diarrhea, but patients may also exhibit nausea, vomiting, abdominal pain and myalgia.

**Bacteremia during pregnancy and fetal granulomatosis infantiseptica.** Infections occur most commonly during the third trimester and patients may present with fever, chills and muscle/joint/back pain associated with bacteremia. In cases of back pain and fever, pyelonephritis is an important differential diagnosis. The course of disease may be mild to severe, and may or may not lead to infection of the fetus. However, premature labor is common and 22% of infections lead to stillbirth. Antibiotic therapy during gestation can allow for the birth of a healthy infant.

In the fetus, untreated infection induces “granulomatosis infantiseptica,” a condition characterized by abscessation and granuloma formation throughout the body (liver, spleen, lungs, kidney, brain). Infection may be associated with fetal death or birth of a weak infant. Affected infants that are born alive require intensive antibiotic and supportive care, but case fatality rates can still be very high even with aggressive therapy.

**Sepsis.** Infection may produce a sepsis syndrome in humans of any age, but this is most common in neonates that acquire the infection perinatally and in immunocompromised patients. In cases of fetal infection, the mother may be asymptomatic, but *L. monocytogenes* will often be isolated from the birth canal. This clinical presentation may mimic Gram (-) sepsis with hypotensive shock.

**Meningoencephalitis.** This is the most common outcome of bacteremia with *L. monocytogenes*, and as with the sepsis syndrome, occurs most often in neonates and immunosuppressed patients. Clinical symptoms and signs may vary from subtle, with low-grade fever, inappetence, and neck pain (and bulging fontanelles in infants) to fulminant disease with coma. Patients may also manifest cerebritis with fever, headache, nausea and paralysis, or fulminant rhomboencephalitis. In all of these circumstances, CSF analyses (cells, protein, glucose) may or may not be remarkable, and CSF cultures may or may not yield *L. monocytogenes*.

**Other sites of infection.** Ulcerative skin lesions have been documented in veterinarians exposed to infected fetuses. In addition, all of the following have been documented in association with *L. monocytogenes* infections: conjunctivitis, anterior uveitis, lymphadenitis, endocarditis, pericarditis, myocarditis, arthritis, osteomyelitis, CNS abscesses, cholecystitis, splenic abscess and peritonitis.
**Agricultural Factors**

*Listeria monocytogenes* is very widely distributed in the environment (soil, water, pasture plants) and is acquired more commonly from the environment than from direct contact with animals. However, infected animals are the most common source of environmental contamination. The organism is shed in the feces of both clinically and subclinically infected animals, particularly ruminants, and can survive for months to years in the soil. Another potential source of the organism on a farm is silage feed. *Listeria monocytogenes* cannot replicate at pH<5, which means that it does not replicate in properly prepared silage. However, *L. monocytogenes* can replicate efficiently in poorly fermented silage with pH>5. Finally, although infected animals are a major source of *L. monocytogenes*, it should also be appreciated that 1-30% of apparently healthy human beings (especially pregnant women) can also be shedding the organism in their stools at any given time.

Clinically, listeriosis is of most significance in ruminants (cattle, sheep, goats), but monogastrics (e.g., horses, dogs) are also less commonly affected. Infection in ruminants usually occurs via ingestion of the organism from feed or the environment, but it can also enter through the nasal mucosa, conjunctiva and skin wounds. The clinical presentations in animals are very analogous to those in humans. The most common form of disease in ruminants is encephalitis, manifest by circling, facial paralysis, nystagmus, dysphagia, head pressing and blindness. The case fatality rate in this encephalitic form of disease is very high. Transplacental infection leads to fetal infection and abortion, and as in humans, neonates may develop septicemia. Finally, *L. monocytogenes* can cause mastitis in ruminants, and there may be prolonged shedding in the milk, which can be a source of infection for humans.

**Management Issues for Human Health**

**Diagnosis.** The diagnosis of listeriosis requires isolation of *L. monocytogenes* from clinical specimens that are normally considered sterile. Isolation from stool specimens is not considered proof of gastrointestinal infection since 1-30% of healthy persons may shed the organism from their gastrointestinal tract. In contrast, the organism is considered a frank pathogen if found in blood, synovial fluid, peritoneal fluid, or cerebrospinal fluid. Standard microbiologic methods found in most clinical laboratories will lead to the isolation and identification of the organism. To date, other methods to directly detect *L. monocytogenes* such as polymerase chain reaction have not shown routine clinical utility.

Antibodies to listerolysin O are used in epidemiologic studies for the identification of individuals that may have been infected from a point source due to ingestion of contaminated food products. Such individuals may present with gastroenteritis or be asymptomatic. However, antibody levels to listerolysin O do not rise very quickly. Thus, serologic methods are of no benefit in diagnosing acute listeriosis.

**Treatment.** Ampicillin is considered to be the drug of choice for treating infections caused by *L. monocytogenes*. However, there are no controlled clinical trials to prove this assertion. Based on animal models and synergy shown with *in vitro* studies, most infectious disease experts recommend the combination ampicillin and gentamicin when treating serious listerial infections (i.e. bacteremia in an
immunocompromised patient, as well as persons with either meningitis or endocarditis). In persons that are intolerant of β-lactams, trimethoprim-sulfamethoxazole is considered to be the best alternative.

Because *L. monocytogenes* has a high affinity for the central nervous system, high “meningitis” doses of antibiotics should be used whenever this organism is isolated from blood. Since impaired cellular immunity is considered to be a risk factor for listeriosis, corticosteroids should definitely be avoided in patients infected with this organism. Persons presenting with meningitis should be monitored initially in the intensive care unit and may require intubation and mechanical ventilation to protect their airway.

**Prevention.** In 1992, the CDC published dietary recommendations for preventing foodborne listeriosis. The recommendations for all persons included thoroughly washing raw vegetables before eating, thoroughly cooking raw food from animal sources, avoiding consumption of unpasteurized dairy products, and keeping uncooked meats separate from other food stuffs. Additional recommendations for pregnant women and immunocompromised persons included avoiding consumption of soft cheeses and reheating leftover foods until steaming hot.

In 1989, the United States Department of Agriculture began a surveillance program designed to detect *L. monocytogenes* in ready-to-eat meat. This zero-tolerance policy has helped decrease the number of cases of listeriosis encountered in the United States. Just as important, the use of trimethoprim-sulfamethoxazole in immunocompromised persons (i.e. transplant recipients and persons with AIDS) has no doubt protected this high-risk cohort from developing many serious infection with *L. monocytogenes*.

**Regulations**

By Wisconsin law, listeriosis in humans is considered a Category II Reportable Disease. Identification of a case or suspected case must be reported to the patient’s local health officer within 72 hours by submitting an Acute and Communicable Disease Case Report (DPH 4151) or by other means.

Listeriosis is not a reportable disease in animals in Wisconsin.
Selected References


Milker’s Nodules

Definition of the Problem

Milker’s nodules (also known as “paravaccinia” and “pseudovaccinia”) are cutaneous lesions caused by infection of people with poxviruses of bovine origin. These are relatively benign, self-limiting lesions, but it is important to recognize and differentiate them from other cutaneous conditions.

The Etiologic Agent. The primary cause of milker’s nodules in the United States is pseudocowpox virus. This is a parapoxvirus of cattle in the same family as bovine papular stomatitis virus and contagious ecthyma virus/contagious pustular dermatitis virus, which is the causative agent of orf in humans. As a group, the parapoxviruses are morphologically distinct from the orthopoxviruses (e.g., smallpox virus, vaccinia virus, cowpox virus, monkeypox virus) and characteristically elicit a weak immune response by the host. Because of this, parapoxvirus lesions may be persistent and slow to heal.

Pathophysiology and Clinical Presentation

Pathogenesis. Pseudocowpox virus infections occur through contamination of skin wounds or abrasions with the virus. Viral replication is restricted to epithelial cells of the skin and there is no systemic reaction.

Clinical Disease in Humans. Milker’s nodules occur most commonly on the fingers or hands (less commonly arms) of people who have had contact with lesions on an infected cow or, potentially, from contaminated equipment or bedding in the infected animal’s environment. Following an incubation period of several days, the lesions begin as an erythematous papule, possibly with associated vesicles. This progresses over a period of weeks to form a reddish blue-to-brown firm nodule. In some cases there may also be suppuration and scabbing. The lesions eventually heal without a scar, but this may take as long as 6 weeks, and the lesions may be quite painful. In immunocompromised persons, the lesions may be larger and take many months to heal.

Agricultural Factors

Pseudocowpox virus is a pathogen of cattle that is found sporadically throughout the world, including the United States. Lesions on infected animals occur on the udder and teats and may be spread from cow-to-cow by the hands of milking personnel. Clinically, the disease is similar to that described for humans except that the individual lesions heal more rapidly (7-10 days) and more typically suppurate and scab. Lesions may also be present in the mouths of calves that nurse infected cows. This is primarily a concern in beef cattle cow-calf herds on range. In contrast, dairy calves rarely nurse directly from their dams in today’s management systems. Lesions similar to those of pseudocowpox occur when cows are infected with cowpox virus. Cowpox is an orthopoxvirus similar to vaccinia virus. It is not thought to be present in the United States. Its primary geographic distribution is Europe and Asia.
Management Issues for Human Health

**Diagnosis.** The diagnosis of milker's nodules is based on the clinical presentation (i.e. vesicles that progress to pustules occurring on the hands and arms of persons with direct animal contact). Definitive diagnosis may be made by isolating the virus in tissue culture followed by electron microscopic identification.

**Treatment.** There is no specific antiviral therapy. Treatment consists of symptomatic relief of the itching and pain that may accompany the lesions.

**Prevention.** Milker's nodules may be prevented by use of gloves and frequent hand washing when persons come into direct contact with animals. In most cases, this is impractical because the occupation of at-risk persons requires frequent animal contact.

**Regulations**

Neither Milker’s nodules nor pseudocowpox virus infection in cattle are reportable in Wisconsin.

**Selected References**


Orf

Definition of the Problem

“Orf” is a cutaneous disease in humans caused by infection with a parapoxvirus from animals. Although the diseases in animals and humans are clinically similar, they are identified by different names. Orf is the name for disease as it occurs in humans, while in sheep and goats it is called “contagious ecthyma” or “contagious pustular dermatitis.” This is a common infection in sheep and goats and among those who’s occupations bring them in contact with infected animals (farmers, veterinarians, abattoir workers, shepherds and sheep shearers). In fact, in a recent study in the United Kingdom, 23% of people employed or living on a sheep farm had had orf at some point in their lifetimes.

Pathophysiology and Clinical Presentation

Pathogenesis. Infections in humans occur through contamination of skin wounds or abrasions with the virus. Because the virus persists for prolonged periods of time (months) in the dried scabs from animal lesions, infection may occur indirectly through contact with contaminated fomites, bedding etc.

Clinical Disease in Humans. Viral replication is primarily restricted to epithelial cells of the skin, but unlike milker’s nodules, some patients with orf may also develop regional lymphadenopathy, and lesions of the conjunctiva may be quite debilitating. After an incubation period of 3-7 days, a papule develops at the site of inoculation. The papule typically vesiculates and produces a weeping, pruritic and/or painful, red-to-purple colored nodule of several centimeters in diameter with central umbilication. The lesions occur most commonly on the fingers and hands and generally take 3-6 weeks to heal. Lesions may be solitary (more commonly) or multiple, and opportunistic secondary bacterial infections may cause suppuration and scabbing.

Agricultural Factors

Contagious ecthyma/contagious pustular dermatitis virus is an infection of domestic sheep and goats, as well as non-domestic herbivores such as deer, reindeer, musk oxen, alpacas and camels. The lesions in infected animals are most commonly found around the lips. They progress to become ulcerative with overlying scabs. The pain associated with the lesions makes it difficult for the animals to eat, thus causing general debilitation. Lesions may also occur on the udder and teats (due to mechanical transmission via nursing by lambs/kid goats), the vulva, and the periorbital regions and occasionally on the legs. These lesions are associated with much greater morbidity than the lesions of pseudocowpox in cattle.

Sheep and goats are immunized against contagious ecthyma by intentionally scarifying live, virulent virus into an abnormal site on the body, typically the skin of the inner thigh. This is done with the idea that the scabby lesion at this site is not debilitating, and recovery is associated with an immune response that will then prevent development of oral lesions if they are exposed by the oral route in the
future. Inadvertent needle sticks with this live virus vaccine also pose a risk for human infection.

**Management Issues for Human Health**

**Diagnosis.** Similar to milker’s nodules, the diagnosis of orf is based primarily on the clinical presentation (i.e. vesicles that progress to pustules occurring on the hands and arms of persons with direct animal contact). The differential diagnosis should include cutaneous malignancies, milker’s nodules and early cutaneous anthrax. Milker’s nodules are generally smaller and less aggressive in nature than the lesions seen with orf. Also, the black eschar that occurs in the later stages of cutaneous anthrax is not typical of orf. Definitive diagnosis of orf is made by isolating the virus in tissue culture followed by electron microscopic identification.

**Treatment.** There is no specific antiviral therapy. Treatment consists of symptomatic relief of the itching and pain that may accompany the lesions.

**Prevention.** Similar to milker’s nodules, orf may be prevented by wearing gloves to avoid contact with animal lesions.

**Regulations**

Neither orf in humans nor contagious ecthyma in animals are reportable diseases in Wisconsin.
Selected References


**Q Fever**

**Definition of the Problem**

Q fever is an occupational disease of farmers, veterinarians, abattoir workers and others who work with animals, animal products (e.g., contaminated hides) and particularly reproductive tract tissues. Human infections may occur as sporadic cases or in outbreaks, and may present over a range of severity from mild, self-limiting flu-like illness to endocarditis or meningoencephalitis.

The Q stands for “query,” reflecting the disease’s unknown etiology when first recognized in Brisbane Australia in 1935. It is now known to be caused by a rickettsial organism that is maintained in nature by tick transmission (it has been recovered from at least 40 species of ticks) among small mammal, rodent and possibly bird reservoir hosts. The agent may initially be introduced into domestic animal populations (or theoretically, but rarely, directly to people) by ticks. However, it is most commonly transmitted between domestic animals and from domestic animals to people through aerosolization of the organism from placental tissues. The organism is also shed in the milk of infected animals, so consumption of unpasteurized milk poses a risk, but infectivity is far less by this route. Reports of human-to-human transmission are extremely rare, but the organism has been isolated from human milk and human placental tissues, and there are reports of transmission to physicians during abortion procedures and autopsies.

**The Etiologic Agent.** *Coxiella burnetii* is an extremely contagious rickettsial-like organism. As little as a single organism is potentially able to initiate infection via aerosols. As such, it has been investigated as a potential biowarfare/bioterrorist agent, and extreme caution is necessary for anyone handling reproductive tract tissues of suspect animals. *Coxiella burnetii* is also resistant to inactivation in the environment. As such, infections can occur indirectly by inhalation of the organism from contaminated clothing, animal bedding or soils. By way of example, hundreds of people in Switzerland who lived along a road used to herd sheep to pasture were infected in 1983.

**Pathophysiology and Clinical Presentation**

**Pathogenesis.** Following inhalation, replication in the lungs leads to seeding of the bloodstream and riskettsemia. This allows for spread throughout the body. *Coxiella burnetii* is a facultative intracellular pathogen that survives and replicates in phagolysosomes of phagocytic cells. It is estimated that only about _ of infected patients develop clinical illness.

**Acute Q fever Clinical Presentation.** Following an incubation period of 2-4 weeks, the most common form of Q fever is a self-limiting, acute, flu-like illness with sudden onset of fever, chills and sweats, malaise, myalgia and possibly nausea. Patients often report headaches that are remarkable for their severity and association with retro-orbital pain. Infection may also involve the lungs, with or without pulmonary symptoms. Inspiratory crackles may be appreciated on auscultation. The most common radiographic finding is pleural-based opacities. Only approximately 1/3 of patients with pulmonary Q fever will have pleural effusion and/or leukocytosis, and only about 1/4 of patients present with a dry, non-productive cough.
Chronic Q fever Clinical Presentations. Coxiella burnetii infections may also present with more chronic courses of disease affecting a variety of organ systems. These chronic manifestations may follow soon after acute Q fever, or may not develop until as long as 20 years after initial infection. Endocarditis with large numbers of foamy macrophages in valvular vegetations (the aortic valve most commonly, followed in frequency by the mitral valve) is the most common form of chronic Q fever. Arterial emboli may occur as complications of endocarditis, and patients may require valve replacement surgery. Hepatitis can also be a frequent complication of Q fever (61.9% of all cases in one study in France), with or without specific clinical symptoms of hepatic disease. Finding “doughnut granulomas” (an outer fibrin ring with a central lipid vacuole) on histopathologic examination of liver biopsies is suggestive of Q fever. Less common chronic forms of Q fever include meningitis and/or encephalitis (generally <1% of cases), possibly with seizures or coma, and pericarditis, osteomyelitis and optic neuritis. Finally, C. burnetii infection should be considered in immunocompromised patients who present with fever of unknown origin and who have histories suggestive of potential exposure.

Agricultural Factors

Infection of domestic animals with C. burnetii is most often subclinical, but may be associated with abortion. Following infection, the organism may persist in lymph nodes and the mammary glands. During pregnancy, the organism replicates to very high titer in the placenta and people are then most commonly exposed while assisting with delivery of the neonate or disposing of the placenta and associated reproductive tract fluids. The animals that pose the greatest risk for exposure of human beings are sheep and goats, but cattle and even cats and dogs must be considered as sources of the organism. Regarding pet animals, cases of Q fever have occurred among people playing poker in the room where a cat was giving birth, and there are at least 2 family outbreaks associated with parturient dogs. In each case, a subgroup of the litters of puppies or kittens died shortly after birth, although as with ruminants, infections in dogs and cats are most often subclinical. Recent examples of Q fever cases associated with infections in farm animals include:

- Ten people who adopted goats from a humane society in San Mateo County, California in 1996 developed Q fever.
- Twenty five percent of the residents of a small town in Germany were infected in association with lambing time in 1996.
- Twenty six abattoir workers were infected in one town in Australia in 1997, and another outbreak occurred among 24 abattoir workers in 1998.
- A large-scale outbreak of abortions in goats and infections in 37% of the 179 farm personnel working with those goats occurred in Newfoundland in 1999.
- A similar outbreak occurred among goats and goat farm personnel in Wyoming in 2001.
- Three workers involved in the foot and mouth disease culling procedures in the United Kingdom in 2001 contracted Q fever.
The risk of contagion from infected sheep and goats cannot be over-estimated. Control procedures to reduce spread of C. burnetii during an outbreak in sheep and goats may include:

- Only allow the animals to give birth inside a building so as to control aerosol spread and prevent mechanical dispersal of the organism by birds.
- Keep ewes/nannies and lambs/kids indoors for 14 days after parturition to prevent contamination of the farm grounds.
- Collect placentas and stillborn fetuses in sealed containers for disposal.
- Compost contaminated straw and feces under wind- and weather-proof plastic for 2 years.

**Management Issues for Human Health**

**Diagnosis.** The diagnosis of Q fever is difficult because the disease can present in many different ways. Persons may be asymptomatic or have a self limited febrile illness that resolves after 2 weeks. More serious forms of the disease include pneumonia, osteomyelitis, Q fever in infancy, Q fever in the immunocompromised host, hepatitis, endocarditis, or a number of central nervous manifestations, including encephalitis, dementia, and aseptic meningitis. Therefore, the presumptive diagnosis is based on clinical suspicion (i.e. any of the above presentations together with an appropriate animal exposure).

Confirmation of the diagnosis of Q fever is usually accomplished through serologic methods because few clinical laboratories have the resources and experience to work with the organism. Furthermore, C. burnetii is highly infectious and tissues from patients with Q fever should be processed under biosafety level 3 conditions.

Serologic methods used to diagnose Q fever include enzyme linked immunosorbent assays as well as the microagglutination, complement fixation, and microimmunofluorescence tests. Of these, complement fixation is most commonly used. A fourfold rise in IgG titer between acute and convalescent serum specimens is considered diagnostic. Specific IgM should not be used because it may persist for over 2 years after the acute infection. Persons who have chronic Q fever infections have much higher antibody titers than persons with the milder acute illnesses associated with C. burnetii. Thus, a phase 1 IgG titer over 1:200 is considered to be diagnostic of chronic Q fever.

Pathologic specimens may also be useful in diagnosing Q fever. Liver specimens in persons with chronic hepatitis due to C. burnetii demonstrate characteristic doughnut granulomas. In addition, microscopic examination of vegetations found in patients with Q fever endocarditis show a subacute and chronic inflammatory infiltrate with many large foamy macrophages. The organisms are readily seen in these specimens when electron microscopy is used to augment the usual pathology stains and studies.

**Treatment.** Treatment of infection due to C. burnetii depends on the clinical manifestation. Pneumonia and hepatitis usually respond to monotherapy with doxycycline 100 mg daily for a period of 2 weeks. In contrast, chronic Q fever infections such as osteomyelitis and endocarditis typically require a prolonged course of doxycycline combined with rifampin or ciprofloxacin. Some authors have treated patients with Q fever endocarditis for 2 years and valve replacement may also be required. The
response to antibiotic therapy in chronic infections is gauged by improvement in clinical signs and symptoms together with a normalization of the erythrocyte sedimentation rate and resolution of anemia. In addition, IgG phase I antibody titers should fall to less than 1:800 while IgM and IgA antibody titers should both be less than 1:50 by micro-immunofluorescence.

**Prevention.** An experimental vaccine developed by USAMRIID is available for laboratory workers at high risk of *C. burnetii* exposure. However, the vaccine is not commercially-available for veterinarians, farmers, or abattoir workers at this time. Moreover, any laboratory worker being considered for vaccination should first be tested for immunologic evidence of previous, potentially asymptomatic exposure to *C. burnetii* because vaccination in such individuals may lead to severe local vaccine reactions.

Control of ticks and other biting arthropods that feed on sheep, goats and cattle may also help to decrease the incidence of *C. burnetii* infection. In Cyprus, the incidence of infection among goats and sheep with this organism was decreased by strict adherence to a program that required isolation of affected dams, disinfection of the premises, and destruction of any aborted materials. Human cases in research facilities may be prevented if only seronegative sheep are utilized in the research facility. Since person-to-person spread is exceedingly rare, hospitalized patients need not be placed in isolation. Finally, all consumption of unpasteurized milk products should be discouraged.

**Regulations**

By Wisconsin law, Q fever in humans is considered a Category II Reportable Disease. Identification of a case or suspected case must be reported to the patient’s local health officer within 72 hours by submitting an Acute and Communicable Disease Case Report (DPH 4151) or by other means.

Similarly, Wisconsin law also requires that Q fever in animals be reported to the State Veterinarian within 10 days of diagnosis.
Selected References


Rabies is one of the most highly feared infectious diseases worldwide. It is also in many ways the classic example of a zoonotic disease, since with the exception of rare laboratory or iatrogenic cases, infection is always associated with contact with an infected domestic or wild animal. There were 627,000 cases of fatal rabies in humans around the world from 1976-1995, and 5-6 million people need to be immunized against rabies annually. Epidemiologically, the major animal vectors of rabies virus vary in different regions of the world, e.g. wolves in Russia, foxes in northern Europe, the vampire bat in South America, and bats, jackals, mongoose and particularly feral domestic dogs in large regions of India, Africa, Central America and Mexico. Dogs account for 99% of human rabies around the world, although not in developed countries because of the success of canine rabies vaccination programs over the last several decades. In the United States, the major vectors of rabies today are wild animals and the relative importance of different species varies by geographic region:

- raccoons in the Eastern United States
- There has been a very serious problem with raccoon rabies on the eastern seaboard of the United States since the late 1970s. This began with the importation of raccoons from Florida to the Central Atlantic states for hunting. The epizootic then spread extensively up the coast and into New York and New England, westward into northeastern Ohio (since 1997) and northward into Ontario (since July 1999).
- skunks in the Midwest and California
- arctic red foxes in northern N.Y. and Alaska
- grey foxes in Texas, Arizona and New Mexico
- coyotes along the Texas/Mexico border
- bats throughout the United States
- In the United States, bats have become increasingly implicated as a primary source of infection for humans. From 1990-2000, 32 cases of rabies in humans were diagnosed in the United States, 24 of which were caused by bat rabies virus variants, and in virtually all cases there was no known exposure. This is due to the minute nature of bat bite wounds and the potential for bites to occur while people are sleeping. In particular, the majority of recent human cases of bat rabies in the United States have been associated with silver-haired bats. This is a fairly uncommon bat species, but data indicates that the strain of rabies carried by silver-haired bats is uniquely able to replicate efficiently in skin cells. As such, this strain of virus may be able to set up infection in the skin after a shallow bite that doesn’t reach to the preferred site of virus replication, the underlying muscle. Of local interest, the first human rabies case in Wisconsin in over 40 years occurred in Reedsburg in 2001 and was due to infection with the silver-haired bat variant of rabies virus.

Each of the primary animal reservoir species harbor a specific, evolutionarily distinct variant of rabies virus. Thus, the origin of rabies viruses isolated from clinical patients can be traced by antigenic or sequence analysis. However, it is critically important to realize that rabies viruses from a given wild animal reservoir species can spill over into other wild animals (e.g., raccoon rabies infecting skunks in the eastern United States) and domestic animals. Thus, although we no longer have canine-origin
“street rabies” in this country, dogs and other domestic animals can develop rabies through contact with wild animals and then pose a risk for infection of humans.

**The Etiologic Agent.** Rabies virus is a bullet-shaped, enveloped, (-) sense RNA virus. The fact that the virus is enveloped is important for treatment and control because it makes the virus highly susceptible to inactivation with soaps and detergents. Rabies virus can be readily isolated and cultivated in cell cultures and by intracerebral injection of mice.

**Pathophysiology and Clinical Presentation**

**Pathogenesis.** Transmission of rabies virus occurs primarily via bite wounds. Rarely, infection may be able to occur by contamination of an accidental break in the skin or possibly even by inhalation of aerosolized virus in bat caves or in laboratory settings. The incubation period is dependent on many variables, including the site on the body at which the bites occurs. The more distal the bite is on the body (i.e., the further away from the CNS), the longer the incubation period (10 days to 12 months, but usually less than three months). However, the incubation period is also affected by factors such as the degree of innervation of the inoculation site, the severity of the inciting wound and other factors. Following the bite, initial virus replication occurs in myocytes at the site of entry (or possibly within the epithelium of the skin in the case of silver-haired bat bites). Thereafter, the virus gains entrance to peripheral nerves and moves up the nerve trunks in the axoplasm to the dorsal root ganglia, the spinal cord and finally to the brain. Replication in the neuronal cell bodies (especially in the hippocampus in carnivores and the Purkinje cells of the cerebellum in ruminants) occurs, followed by centrifugal spread down the cranial nerves to the salivary glands and virus shedding in saliva. Spread to the salivary glands and shedding can occur several days prior to the onset of clinical signs, hence the use of a 10 day quarantine and observation period to see if biting animals are going to develop neurologic signs suggestive of rabies.

**Clinical Disease in Humans.** Classical signs and symptoms of rabies in human beings include headache, agitation, delirium, dysphagia, hallucinations, seizures, paralysis and coma. However, it can be very dangerous to think in terms of “typical” presentations for rabies, since the initial clinical complaints can be highly variable. For instance, a review of just 5 human patients who developed rabies in the United States in 2000 were described in a Morbidity and Mortality Weekly Report as having presented with pain and paraesthesia in one arm, pain in the lower back and abdomen, intractable vomiting with hematemesis and chest pain. With such presentations, rabies may not even be considered as a differential diagnosis. While the outcome for the presenting patient may not be altered by a delay in the recognition of rabies, delays may impede epidemiologic tracing of additional potential cases and increase potential exposure of health care providers.

**Agricultural Factors**

Rabies in domestic animals has decreased remarkably over the past several decades through vaccination against canine street rabies and the development of rabies vaccines for livestock as well (although the later vaccines are not universally and widely used). Nonetheless, rabies continues to occur in small numbers of domestic animals in Wisconsin every year. In 1999-2001, there were 4 dogs, 3 horses and 6
cows diagnosed with rabies in Wisconsin. (Along with these were 15 rabid skunks and 22 rabid bats.) In animals, rabies is often clinically divided into “dumb” and “furious” forms, though as in humans, there can be substantial variability in clinical presentations. Dumb rabies (traditionally said to occur most commonly in ruminants and horses) is characterized by changes in voice (howling or bellowing), pharyngeal paralysis with drooling and dysphagia, muscle tremors and progressive paralysis, ultimately resulting in coma and death. Furious rabies (traditionally said to occur most often in dogs and cats) is characterized by abnormal, unprovoked aggression toward other animals or people, excessive drooling and dysphagia, disordered wandering and sometimes attempts to break into dwellings, ataxia, seizures, coma and death.

Management Issues for Human Health

**Diagnosis.** The diagnosis of rabies is easy to make when a nonimmunized person presents with hydrophobia after being bitten by a rabid dog that has been quarantined. Unfortunately, most human cases in the United States are not nearly that straightforward. Rabies should be suspected on clinical grounds whenever a patient is found to have unexplained focal and progressive neurologic findings, particularly if there is a component of encephalitis present. However, paralytic rabies may mimic transverse myelitis or acute inflammatory polyneuropathy.

During the prolonged incubation period, no diagnostic studies are of any benefit. Once symptoms begin, standard laboratory tests cannot distinguish rabies from other causes of encephalitis. Imaging studies of the central nervous system will be normal. Cerebrospinal fluid specimens may show a normal glucose level, a mild pleocytosis (5-30 cells per mm³), and a modest elevation in protein (less than 100 mg/dl). Thus, a biopsy specimen may be helpful in confirming the diagnosis if there is no history of an animal bite. In humans, the best place to obtain a skin biopsy is the nape of the neck just above the hairline. Since the virus tends to congregate in hair follicles, a direct fluorescent antibody assay of this area will be positive in most cases (initially, 50% with a rising percentage as symptoms progress).

Alternatively, rapid fluorescent antibody focus inhibition testing has been found to be of benefit in some cases. This test detects neutralizing rabies antibody which are first found in untreated persons by day 6 of clinical illness. Nearly all patients will have a positive assay by day 15 of clinical illness. However, the reverse transcriptase-polymerase chain reaction has now emerged as the diagnostic test of choice for suspected cases of human rabies. This test may be performed on cerebrospinal fluid, saliva or tissue samples. Moreover, subsequent sequence analysis of the PCR amplicon allows for more specific determination of geographic and host species origin of a specific rabies virus than other available tests.

**Treatment.** The key to rabies prevention is actually wound care since up to 90% of the risk may be reduced by this simple measure. Thorough washing with a 20% soap solution should be done followed by irrigation with povidone-iodine solution. The use of rabies vaccines and rabies immune globulin (RIG) for post-exposure prophylaxis depends on the type of animal species and type of exposure. The Advisory Committee on Immunization Practices (ACIP) updated the rabies post-exposure recommendations in 1999. It is now recommended that the bite site be infiltrated with the full dose of
RIG if it is anatomically feasible. In addition, post-exposure prophylaxis should be instituted no matter when the bite occurred. The following tables show the current ACIP guidelines. Once symptoms have begun, care is supportive since there is no specific antiviral medication that effectively treats rabies virus.

### Rabies Post-exposure Prophylaxis Guide

<table>
<thead>
<tr>
<th>Animal Type</th>
<th>Evaluation and Disposition of Animal</th>
<th>Post-exposure Prophylaxis Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, cats, and ferrets</td>
<td>Healthy and available for 10 days’ observation</td>
<td>Persons should not begin prophylaxis unless animal develops clinical signs of rabies</td>
</tr>
<tr>
<td></td>
<td>(During the 10 day observation period, begin post-exposure prophylaxis at the first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.)</td>
<td></td>
</tr>
<tr>
<td>Skunks, raccoons, foxes, and most other carnivores; bats</td>
<td>Regarded as rabid unless animal proved negative by laboratory tests</td>
<td>Consider immediate vaccination</td>
</tr>
<tr>
<td></td>
<td>(The animal should be euthanized and tested immediately. Holding for observation is not recommended. Discontinue vaccine if immuno-fluorescence test results of animal are negative.)</td>
<td></td>
</tr>
<tr>
<td>Livestock, small rodents, lagamorphs (rabbits and hares), large rodents (woodchucks and beavers), and other mammals</td>
<td>Consider individually</td>
<td>Consult public health officials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require anti-rabies post-exposure prophylaxis.</td>
</tr>
</tbody>
</table>

Adapted from *MMWR 1999; 48 (RR-1):1-21.*
<table>
<thead>
<tr>
<th>Vaccination Status of the Exposed Person</th>
<th>Treatment Recommendations</th>
<th>Post-exposure Prophylaxis Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not previously vaccinated</td>
<td>Wound cleansing</td>
<td>All post-exposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidone-iodine solution should be used to irrigate wounds.</td>
</tr>
<tr>
<td>Rabies Immune Globulin (RIG)</td>
<td></td>
<td>Administer 20 IU/kg body weight. If anatomically feasible, full dose should be infiltrated around the wounds and any remaining volume should be administered IM at an anatomic site distant from vaccine administration. Also, RIG should not be administered in same syringe as vaccine. Because RIG might partially suppress active production of antibody, no more than recommended dose should be given.</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>Human diploid cell vaccine (HDCV), rabies vaccine adsorbed (RVA), or purified chick embryo cell vaccine (PCEC) 1 ml, IM in the deltoid area (use deltoid only unless patient is a child, in which case the outer aspect of the thigh may be used), one each on day 0, 3, 7, 14, and 28.</td>
</tr>
<tr>
<td>Previously vaccinated</td>
<td>Wound cleansing</td>
<td>All post-exposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidone-iodine solution should be used to irrigate wounds.</td>
</tr>
<tr>
<td>Rabies Immune Globulin (RIG)</td>
<td>RIG should not be administered.</td>
<td></td>
</tr>
<tr>
<td>Vaccine</td>
<td>HDCV, RVA, or PCEC 1 ml, IM (deltoid area), one each on days 0 and 3.</td>
<td></td>
</tr>
</tbody>
</table>

Prevention. The cornerstone of prevention is to avoid being bitten by an animal, together with immunization of cats and dogs. In the United States, 3 year duration-of-immunity vaccines are recommended for cats and dogs. All animal rabies vaccines must legally be administered by a veterinarian, since improper vaccination may result in lack of immunity. Vaccination of livestock is recommended in areas where the prevalence of rabies is high. Immunization of wild animals with specifically approved vaccine products is sometimes used to curb the incidence of rabies in specific areas.

Pre-exposure vaccination of people is limited to persons at high-risk of exposure. This includes veterinarians, animal control personnel, laboratory workers, spelunkers, and persons traveling to countries where the incidence of rabies is high and access to health care is low. A series of three intradermal or intramuscular inoculations on days zero, 7, and 21 or 28 with any of the three available rabies vaccines offers excellent protection. However, a booster dose every 2-3 years is recommended for any person that is at risk of continued exposure.

Regulations

Rabies in both animals and humans is reportable in Wisconsin. By Wisconsin law, rabies in humans is considered a Category I Reportable Disease. Identification of a case or suspected case must be reported immediately to the patient’s local health officer by phone, and in writing within 24 hours by submitting an Acute and Communicable Disease Case Report (DPH 4151). Similarly, rabies in animals must be reported to the State Veterinarian within 24 hours of diagnosis. Suspect animals may be euthanized immediately and their head submitted for rabies virus testing of the brain, or they may be quarantined and observed for signs of rabies. The specific disposition of suspect animals depends upon whether they are wild or domestic, and among domestic animals whether or not they have been vaccinated and the nature of the potential human exposure.
Selected References

There are a variety of electronic sources for information regarding rabies.

- The CDC National Center for Infectious Diseases rabies homepage is available at http://www.cdc.gov/ncidod/dvrd/rabies, with many links to additional rabies sites.
- The CDC Morbidity and Mortality Weekly Report is an excellent source for specific case presentations of rabies and is available at http://www.cdc.gov/mmwr/
- The Compendium of Animal Rabies Prevention and Control is published yearly in the Morbidity and Mortality Weekly Report and is available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mmwrhtml/r5008a1.htm
- The Wisconsin statutes on animal rabies control can be found in s.95.21 and at http://folio.legis.state.wi.us/cgi-bin/om_isapi.dll?clientID=99194&infobase=stats.nfo&jump=95.21.


Zoonotic agents of gastroenteritis (Campylobacter, Yersinia, Salmonella, Giardia, Cryptosporidium and E. coli O157:H7)

Definition of the Problem

Each of these infectious agents of gastroenteritis can affect both humans and domestic animals. Although these organisms are most commonly acquired by both humans and animals via waterborne or foodborne transmission, domestic animals may pose a direct zoonotic risk.

The Etiologic Agents.

**Campylobacter** are Gram (-), curved, comma- or gull wing-shaped bacilli. They are microaerophilic, slowly growing bacteria that require special media with antibiotics to inhibit the growth of other fecal flora bacteria. *Campylobacter jejuni*, the most important species as a human pathogen, grows best at 42°C. Although this organism may be found in contaminated water and unpasteurized milk products, the major source of *Campylobacter* for humans is contaminated, undercooked poultry meat. Studies have shown that 22-100% of commercially-sold poultry products are contaminated with *C. jejuni*, and this source accounts for 50-70% of all human cases. A concern above and beyond the frequency of contamination is the occurrence of antibiotic-resistance among *Campylobacter* isolates from poultry products. Recent studies have documented 20-84% resistance to antibiotics, including fluoroquinolones. *Campylobacter* bacteria can be part of the normal flora of the gastrointestinal tracts of other species of livestock, including both ruminants and swine, and can additionally infect cats and dogs. As such, direct contact with feces from infected animals is also a risk for zoonotic infection. In fact, living with dogs or cats has been shown to be a specific risk factor for *Campylobacter* infection.

**Yersinia enterocolitica** is a Gram (-) bacillus that will grow on conventional blood, brain heart infusion and MacConkey agars. Virulence of *Y. enterocolitica* is dependent on the presence of V and W antigens and pathogenicity is enhanced by resistance to complement and the ability to penetrate epithelial cells. *Yersinia enterocolitica* is a relatively rare cause of gastroenteritis in humans that is most often acquired through contaminated foods. For instance, there was a large outbreak in Oneida County, NY in 1976 in which 218 school children were infected via chocolate milk. Contaminated chocolate syrup was added after pasteurization of the milk. Infections have also been reported in association with consumption of “chittlins,” a dish prepared most commonly in the southern United States from the large intestines of pigs.

**Salmonella** are Gram (-), facultatively anaerobic bacilli that are best isolated using enrichment (e.g., tetraelementate and selenite F broths) and selective (e.g., MacConkey and SS [salmonella-shigella] agar) media. There are a very large number of serotypes of *Salmonella*, many of which are associated with specific animal sources. However, it should be recognized that *S. typhi* and *S. paratyphi* (the agents of typhoid and paratyphoid fevers) are strictly pathogens of humans and non-human primates.

**Giardia intestinalis/duodenalis** (previously called *G. lamblia*) is a flagellate protozoan that inhabits the intestinal tracts of a wide variety of domestic and wild animals species and causes gastroenteritis in both animals and humans. Infection occurs through consumption of the cyst form of the organism...
(perhaps as few as 10-25 cysts) that is passed in the feces of infected animals. Infections in humans are most commonly waterborne. Backpackers and others pursuing outdoor activities may be infected from what appear to be pristine mountain water sources because of human or animal fecal contamination upstream. The cysts survive well in cold water and are not consistently inactivated by routine chlorination tablet water purification systems - filtration is needed. The second most common mode of infection is person-to-person, e.g. in day-care centers. Thirdly, contact with infected animals can be a direct source for *Giardia* infection of humans since the cysts are infectious when passed in the feces.

*Cryptosporidium parvum* is an extremely important, emerging, protozoal pathogen in humans and domestic animals. It produces a self-limiting, acute diarrheal disease in immunocompetent human beings, but is a leading cause of life-threatening chronic diarrheal disease in immunocompromised patients. Infection occurs by ingestion of oocysts excreted in the feces of animals or other humans. These oocysts are extremely resistant to inactivation in the environment and highly infectious – the median infective dose (determined from human feeding trials) is only 132 oocysts and as few as 10 oocysts may be sufficient. There is no routinely applicable chemical method of inactivation to kill the organism in drinking water and no consistently successful form of therapy for use either humans or animals.

*E. coli* O157:H7 is distinguished from other *E. coli* by its inability to ferment sorbitol and, most importantly, by its production of “shiga-like” toxins (SLT I and II). These toxins were so named because of their similarity to the toxin of *Shigella*, with 5 receptor binding B subunits and one active A subunit. Although *E. coli* are common commensals in the intestinal contents of many species of animals, the O157:H7 organism is of specific concern because human infections involve not only enteritis with watery diarrhea and hemorrhagic colitis, but also a hemolytic-uremia syndrome (HUS) characterized by thrombocytopenia, renal failure, and microangiopathic hemolytic anemia. HUS occurs most commonly following infection of children (2-7% of *E. coli* O157:H7-infected children develop HUS).

**Pathophysiology and Clinical Presentation**

**Pathogenesis.** *Campylobacter jejuni* infection can involve the jejunum, ileum and colon, with edematous and hemorrhagic enteritis lesions. Possible virulence factors include enterotoxins, cytotoxins and cytovinvasion ability, which can lead to bacteremia. A significant sequella of *C. jejuni* infection is the development of immune-mediated Guillain-Barre syndrome (GBS). Evidence suggests that there is antigenic mimicry between the lipopolysaccharides of *C. jejuni* and GM1 gangliosides in human nervous tissue. It is estimated that approximately 1/1000 *Campylobacter* infections results in GBS and that up to 66% of GBS cases have premonitory *C. jejuni* infections. Additionally, GBS that follows *Campylobacter* infection is more severe and more likely to be irreversible. *Campylobacter* infection in humans has also been associated with another immune-mediated disease, Reiter’s syndrome (reactive arthritis and tenosynovitis with accompanying skin lesions, uveitis and urethritis) and also with fatal septic shock in a splenectomized patient, reflecting the potential severity of infection in immunocompromised individuals.
**Yersinia enterocolitica** primarily targets the ileum, inducing mucosal ulcerations, Peyer’s patch necrosis and mesenteric lymphadenopathy. A large inoculum dose (>10^9 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*, and less frequently *Campylobacter* and *Salmonella* infections) may mimic appendicitis (“pseudoappendicitis”). Finally, as with *Campylobacter* infections, *Y. enterocolitica* infection may also lead to immune-mediated phenomena, including Reiter’s syndrome or reactive arthritis.

*Salmonella* bacteria may cross the intestinal wall via invasion through M cells or enterocytes to spread systemically. However, infection at the enterocyte level is responsible for gastroenteritis. Histologically there is inflammation in both the small and large bowels with neutrophil infiltration. Toxic products from invading neutrophils recruited to the site and enterotoxins expressed by *Salmonella* may contribute to the tissue damage and fluid loss across the bowel wall.

The pathogenetic mechanisms employed by *Giardia* and *Cryptosporidium* are fundamentally different from those of the bacterial agents of gastroenteritis. Specifically, these protozoal agents reside and replicate primarily on the mucosal surface of the gut rather than within enterocytes. *Giardia* infections may disrupt the brush border surface of enterocytes, leading to a loss of disaccharidase activity and malabsorption. In addition, the cellular immune response to infection and associated inflammation can lead to flattening of the intestinal villi and subsequent malabsorption. *Cryptosporidium* similarly resides within the microvillous border of enterocytes and the diarrhea may be due to malabsorption or osmotic fluid loss. Histologically, there can be atrophy, blunting or loss of villi and inflammatory infiltrates in the lamina propria.

Compared to other organisms that cause dysentery, the pathogenesis of *E. coli* O157:H7 is unique because of the absence of enteroinvasion and a lack of mucosal inflammation. As stated previously, the O157:H7 strain produces Shiga-like toxins that are cytotoxic to Vero cells. One of these toxins is encoded by a lysogenic toxin-converting bacteriophage. It is thought that these toxins result in endothelial cell death and produce fibrin deposition. In turn this leads to small vessel occlusion and disseminated intravascular coagulation. It is this combination that results in the hemolytic-uremic syndrome (HUS).

**Clinical Disease in Humans.** Each of these infections primarily cause diarrheal disease, although there are differences in the courses of disease in each case. *Campylobacter, Yersinia* and *Salmonella* infections typically induce an acute diarrheal disease following an incubation period of 2-4 days (slightly longer for *Yersinia*). Illness is characterized by fever, nausea, malaise, headache, myalgia and/or abdominal pain. Stools may be loose to watery and may include hematochezia. The course of illness is generally several days to potentially several weeks in duration. *Campylobacter jejuni* rarely also spreads systemically to induce meningitis, endocarditis and septic abortion. (Systemic illness is much more common with *Campylobacter fetus* subsp. *fetus* [a.k.a. *Vibrio fetus*] and *C. hyointestinalis* infections.) *Yersinia enterocolitica* infection has also been associated with exudative pharyngitis and, rarely, pneumonia and lung abscessation. A specific concern with *Salmonella* infections is the potential for development of a long-term carrier state. However, this is a greater problem with
non-zoonotic *S. typhi*. By 3 months following infection, less than 10% of patients are still carrying non-typhoidal *Salmonella* spp., with only 0.2-0.6% of patients progressing to a chronic (> 1 year) carrier state. Serious complications of non-typhoidal *Salmonella* infections include a persistent bacteremia and fever syndrome (especially a concern with two zoonotic *Salmonella*, *S. cholerae-suis*/pigs and *S. dublin*/cattle), endocarditis and 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 and joints.

*Giardia* infection induces both acute and chronic gastroenteritis. The acute phase develops 1-2 weeks following exposure and is characterized by diarrhea (initially watery, but then with more consistency, steatorrhea and a rancid, foul odor), abdominal pain, malaise, nausea, bloating and flatulence. Fever is much less common than with the bacterial infections. Progression to the chronic stage of infection is accompanied by significant weight loss and continued greasy, malodorous diarrhea (sometimes alternating with periods of constipation), malaise and abdominal pain. *Cryptosporidium* infections may also be associated with significant weight loss and the diarrhea may be accompanied by low-grade fever, malaise, nausea and inappetence. The severity and nature of the diarrhea varies among different patients and may vary in severity over time in individual patients. However, in immunocompromised patients, the diarrhea can be persistently severe, with production of >12 liters of fluid stool/day. Infection has also been associated with cholecystitis, pancreatitis and reactive arthritis. Clearance of the organism is extremely difficult in immunocompromised patients and cryptosporidiosis of >30 days duration is part of the CDC case definition of AIDS.

*E. coli* O157:H7 infections are associated with an inflammatory colitis that begins following a 1-8 day incubation period. The disease typically consists of a severe diarrhea associated with abdominal pain and nausea, but little or no fever. When frank blood is absent, stool specimens usually test positive for occult blood. Most people (i.e. more than 95%) with enterohemorrhagic *E. coli* recover spontaneously with no untoward consequences after a 5-10 day illness. However, approximately 5% of children infected with *E. coli* O157:H7 will develop HUS about 5-7 days after the onset of diarrhea. HUS consists of thrombocytopenia, microangiopathic hemolytic anemia, and renal failure. The lack of fever or central nervous system involvement helps to distinguish HUS from thrombotic thrombocytopenic purpura. Persons with HUS are at considerable risk of death from acute oliguric renal failure, bleeding (especially hematuria) and cerebral infarction. For unknown reasons, HUS affects children under 4 years of age more commonly than persons in other age groups.

**Agricultural Factors**

*Campylobacter jejuni* can subclinically colonize the gastrointestinal tracts of ruminants and pigs as a commensal and be shed in their feces. It can also be shed by infected dogs and cats with or without clinical illness in those animals. In addition, other enteric campylobacters can also infect humans and domestic animals (*C. coli*/dogs, pigs, horses; *C. upsaliensis*/dogs and cats) and the systemic campylobacters, *C. hyointestinalis* and *C. fetus* subsp. *fetus*, can be carried by pigs and cattle, respectively.
The most likely animals sources for *Y. enterocolitica* are pigs and dogs. Infections in dogs (rarely cats) can be subclinical or can be associated with acute enteritis. In pigs, *Y. enterocolitica* commonly colonizes the pharynx of pigs as a commensal organism. In one study, there was at least one pig shedding the organism in 92.2% of market swine lots. Humans can become infected through direct contact with infected pigs or through consumption of undercooked pork products.

The feces of virtually any animal (including all of the conventional farm animals, pet animals and many exotic pets) can be a potential source of *Salmonella*. In one study, *Salmonella* could be isolated from 5.5% of horses that had been hospitalized for other reasons. A particularly important source of concern is pigs because of the severity of endocarditis in humans infected with *S. cholerae-suis* infections. Recently, associations are increasingly being recognized between specific *Salmonella* serotypes and contact with specific animal species. These include:

- *S. montevideo* and baby chicks (“Easter chick” outbreaks)
- *S. marina* and iguanas
- *S. java* and *S. poona* and turtles, iguanas and lizards
- *S. tilene* and hedgehogs and sugar gliders
- *S. typhimurium* DT104 and cattle

This association is of particular importance to the topic of rural health. DT104 is a specific “definitive type” (i.e., DT) of *Salmonella* serotype *typhimurium* that has been associated with multidrug antibiotic resistance and serious disease in both cattle and humans. It was first isolated in the United Kingdom in 1984 and was associated with human hospitalization rates approaching 50% and 5% mortality. Cattle mortality approached 40%. In addition, the rate of isolation of DT104 has skyrocketed in the United Kingdom, from 259 human cases in 1984 to 4,006 in 1996. The prevalence of DT104 is also growing in the United States and Canada. In one study in the United States in 1995, 28% of *S. typhimurium* isolates submitted to the CDC for antimicrobial resistance testing exhibited the R-type ACSSuT (ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline) resistance pattern that typifies DT104. In addition, there have been 5 localized outbreaks reported in the United States: one in Vermont, two in Washington and two in California.

The exact role of animals in the epidemiology of *Giardia* infection in humans is unclear. Dogs and cats can clearly serve as a source for contamination of the environment with the organism and must be considered as potential zoonotic risks. The same may be true for cattle, goats, llamas and pigs, although some isolates from these species represent strains that appear to be genotypically distinct and restricted only to livestock, never having been recovered from humans. In 1999, a killed, whole-organism vaccine was approved for use in dogs in the United States and has been shown by the manufacturer to reduce the shedding of *Giardia* cysts after experimental infection. Specifically, 0/20 vaccinated dogs shed cysts on day 42 after infection, compared to 10/10 placebo controls. This vaccine is not, however, widely used.

The domestic animal of most importance as a reservoir of *Cryptosporidium parvum* is cattle. Neonatal calves are infected during the first days of life, leading to clinically important diarrheal disease. Nationally, in a study of 7,369 calves on 1,103 farms, oocysts were detected in the feces of calves on
59.1% of farms, and from 22.4% of all calves tested. More limited studies in Idaho and Maryland found farm seropositivity rates of 56% and 75%, respectively. In a study by Atwill et al. in 1998, 92% of calves 7-21 days of age were shedding the organism, yet their periparturient dams were not, and the organism was not present in the calving stall soil. Where was it? Wood scrapings from the surfaces of the walls and floors of calf hutches, even after cleaning, contained the organism. In Wisconsin, cryptosporidiosis is estimated to claim 20,000 calf lives per year, at a cost of $3 million dollars. Furthermore, in a survey of people here in Wisconsin, it was found that 44% of farmers versus 24% of non-farming neighbors were seropositive for exposure to *C. parvum*. Zoonotic infections are well-documented as risks for veterinary personnel working with infected animals. However, as with *Giardia*, there may be both zoonotic and non-zoonotic aspects to the epidemiology of *Cryptosporidium*. Specifically, there are genotypes of *C. parvum* that are human-specific and are not isolated from animals. Among domestic animals other than cattle, studies have found high rates of seropositivity in horses, but few instances of clinical disease. Pigs can also be both naturally and experimentally infected, but seldom show clinical signs. Dogs (and to a lesser extent cats) can be infected with specific zoonotic genotypes of *Cryptosporidium* and may develop diarrhea. Finally, birds and reptiles can also harbor *Cryptosporidium spp.* and suffer either gastrointestinal (often primarily regurgitation in reptiles) or respiratory disease, but to date only *C. meleagridis* has been shown to be zoonotic.

Cattle present many of the same zoonotic issues for *E. coli O157:H7* as for *C. parvum*. Infection with O157:H7 is subclinical in cattle and the duration of shedding may be quite variable and intermittent, making test and removal control programs impossible at this time. Prevalence estimates vary, but it appears that although a substantial percentage of both dairy herds and beef feedlots have infected animals, the actual number of individual infected animals at any one time is relatively low. Dairy calves and heifers shed the organism more often than adults, with the peak time of infection being 3-18 months of age. Recovery of O157:H7 from beef feedlots is highest in pens from which the cattle have been in the feedlot for the shortest periods of time. As regards the potential for direct animal-to-human transmission via contact with animal feces, two recent studies have demonstrated higher than expected rates of seropositivity to O157:H7 among farm families. In addition, there have been several reported incidents of transmission to children that visited or lived on a farm. In some of these cases, the bacterial isolates from the children and the cows were proven to be identical by pulse field gel electrophoresis (PFGE). Most recently, in May 2000 in Washington and in November 2000 in Pennsylvania, 56 children were infected (19 required hospitalization) through contact with animals during school or family visits to farms. Closer to home, approximately 26 people acquired O157:H7 in August 2001 in association with attendance at a county fair here in Wisconsin in Ozaukee County. Animals other than cattle that may potentially serve as sources of *E. coli O157:H7* include deer, pigs, dogs and horses. In one study involving deer, the organisms isolated from 2 deer and 5 cattle on a ranch in Texas had identical PFGE patterns. In addition, human infection has been associated with consumption of venison jerky, and deer have been experimentally infected and shown to intermittently shed the organism like cattle. As regards pigs, recent human cases of HUS have been associated with swine isolates and a survey of pigs in Japan revealed approximately the same level of infection with O157:H7 in pigs as in the cattle population. The O157:H7 strain has been isolated from two asymptomatic dogs on a farm in Washington (along with the cattle, a horse, two batches of stable flies and biofilms on water troughs on the farm) and there have been reports of dog-to-human transmission in Canada and the U.K., as well as a report of O157:H7 isolation from a veterinary student’s dog in the
United States. In particular, racing greyhound dogs are sometimes fed raw beef and E. coli O157:H7 has been isolated from beef fed to dogs. Finally, there is a single report of infection of a farmer with O157:H7 after caring for a sick horse, from which an identical O157:H7 isolate was obtained.

**Management Issues for Human Health**

**Diagnosis.** The diagnosis of enteric infection with *Campylobacter* species should always be considered whenever a patient presents with an acute diarrheal illness associated with ingestion of raw or undercooked poultry. Direct examination of feces may yield clumps or sheets of the organism with its characteristic shape. Historically, *Campylobacter* species were quite difficult to isolate because the organisms are microaerophilic and require special media and temperature conditions to optimally grow. In modern times, however, almost all clinical microbiology laboratories are capable of isolating the organism using routine protocols for bacterial cultures of the stool.

The diagnosis of enteric infection with *Yersinia spp.* should be considered whenever a patient presents with diarrhea and vomiting, fever, and abdominal pain. As stated above, infection with this organism may mimic appendicitis. *Yersinia spp.* may be isolated from stool, blood, or vomitus but it requires special media to grow. Therefore, clinicians that suspect this organism must notify the laboratory so that appropriate testing is done. Serology is available only through selected research and reference laboratories.

Salmonellosis should be considered when a person presents with diarrhea, fever, abdominal cramps, and vomiting. Typhoid, an illness with an insidious onset characterized by high fever, headache, constipation, malaise, chills and myalgia, may result from infection with either *S. typhi* or *S. paratyphi*. Diarrhea is typically absent and vomiting is usually not severe in typhoid fever. Enteric infection with *Salmonella* species is established by isolating the organism from routine stool cultures. In contrast, typhoid fever often requires isolation of the organism from blood.

The diagnosis of giardiasis should be suspected in persons that present with acute or chronic diarrhea associated with flatulence and bloating. The stool odor is particularly malodorous and the onset of symptoms is often explosive. Strong epidemiologic associations include camping and hiking, contact with children attending day care, and travel to St. Peterburg in Russia. The diagnosis is confirmed whenever the cysts or trophozoites are found in stool specimens. In the past, 3 stool specimens sent for ova and parasite examinations were often required to diagnose giardiasis. However, the *Giardia* antigen enzyme immunoassay requires only one stool specimen and is now widely available in the United States.

Infection with *Cryptosporidium parvum* should be considered when an immunocompromised patient presents with prolonged and severe watery diarrhea. Associated symptoms may relapse and recur, include cramping abdominal pain, fever and vomiting. Importantly, this organism may also affect persons with normal immunity, albeit with less severity. Although there is no single universally accepted diagnostic technique, most clinical laboratories rely on a modified acid-fast stain procedure performed with fecal concentration. Enzyme-linked immunosorbent assays with sensitivities and specificities over 90% are now commercially available. However, the costs of these antibody-based
detection systems is prohibitive.

*E. coli* O157:H7 requires special media to grow; therefore, most clinical laboratories require notification that this organism is being considered in the differential diagnosis whenever a stool specimen is sent for bacterial culture. This requirement alerts laboratory personnel to the need of setting up the appropriate stool cultures for the organism. Shiga toxin testing may be done by special kits. However, all positive isolates should be forwarded to a public health laboratory for confirmation and serotyping.

**Treatment.** The most important aspect of treating enteric infections due to *Campylobacter* species is replacement of a person’s fluid and electrolytes. If dehydration is severe, intravenous fluids may be required to resuscitate a patient. In most cases, however, oral rehydration with glucose and electrolyte solutions will suffice. Antimicrobial therapy has been shown to benefit persons with high fever, bloody diarrhea, or more than eight stools per day. Other persons that may benefit from antibiotic therapy are those that present with worsening symptoms or diarrhea that has been present for more than one week. Oral ciprofloxacin 500 mg twice daily for three days is considered the treatment of choice for moderate-to-severe *Campylobacter* infections. However, the rise in fluoroquinolone resistance suggests that oral azithromycin (500 mg once daily for three days) may supercede the current recommendation in the near future. In contrast to enteric infections, bacteremia and other deep infections require prolonged therapy.

Supportive care is all that is usually needed to treat enteric infections due to *Yersinia* species. However, if septicemia or other invasive disease is present, antibiotic therapy with cefotaxime or gentamicin is indicated. In addition, doxycycline, trimethoprim-sulfamethoxazole and ciprofloxacin have all been used effectively to treat *Yersinia enterocolitica* infections.

Antibiotics are not indicated for most cases of salmonellosis. However, it is prudent to treat these infections if there is extra-intestinal spread. Ciprofloxacin 500 mg twice daily for 5-7 days is considered the treatment of choice. However, numerous other antibiotics (i.e. ampicillin, gentamicin, trimethoprim-sulfamethoxazole and other fluoroquinolones) have also been used effectively. The treatment of typhoid fever requires prolonged therapy with ciprofloxacin (500 mg po bid for 10 days) or a third generation cephalosporin (ceftiraxone 2 g IV for two weeks). When shock is present, dexamethasone should be accompany antibiotic therapy.

Giardiasis is treated with either oral metronidazole (250 mg thrice daily for 5 days) or albendazole (400 mg once daily for 5 days). Because of concern for the fetus, pregnant patients should be treated with paromomycin (500 mg four times a day for 7 days). Clinicians treating persons with refractory illness should consider prescribing a three day course of metronidazole (750 mg thrice daily) combined with quinacrine (100 mg thrice daily).

Clinical trials have failed to demonstrate an effective treatment for cryptosporidiosis. For patients with normal immunity, this does not matter because the disease is generally self-limiting. However, dehydration occasionally mandates hospitalization for fluid resuscitation. In contrast, patients with compromised immunity may develop life-threatening diarrhea. These patients may benefit from
anti-motility agents such as bismuth subsalicylate, diphenoxylate, loperamide and opiates. Supportive care may include intravenous hydration or even total parenteral nutrition. In severe cases, oral paromomycin (1000 mg twice daily for 7 days) may be considered.

Enterohemorrhagic *E. coli* infection due to the O157:H7 strain may cause fever and bloody diarrhea. It is important to document the presence of this organism because antimicrobial agents may enhance toxin release and increase the risk of hemolytic-uremic syndrome. Similarly, anti-motility agents should be avoided because they may prolong the time that toxins remain inside of a person. Therefore, avoiding antibiotics together with supportive care are the mainstays of therapy.

**Prevention.** The cornerstone of preventing these enteric infections is to avoid ingestion of contaminated food or water and contact with potentially infected animals. In most situations, this requires reliable access to clean water and attention to good personal hygiene, especially in food handlers and day care workers. Absolute maintenance of time-temperature standards when handling food is also of utmost importance. Public education related to food safety should emphasize the need to thoroughly cook poultry and ground beef, to designate and use dedicated cutting boards for preparing meat products, and to wash hands frequently. Campers and hikers should be counseled regarding appropriate water treatment protocols to prevent enteric infections, particularly giardiasis and cryptosporidiosis. Standard chlorination fails to eradicate certain pathogens (such as *C. parvum*); in addition, pools and hot tubs are not reliably treated. Thus, the general public should be counseled to avoid swallowing water while bathing or swimming.

In immunocompromised patients, the risk of contracting cryptosporidiosis may be decreased if disposable gloves are used whenever a person contacts human or animal feces. Hand washing after gardening or contact with pets is also beneficial in this high risk group. Although removing a healthy pet is not necessary, any new pets should be older than 6 months of age in order to diminish the risk of infection with *Campylobacter* and *Cryptosporidium* species. Lastly, pets with diarrhea should be immediately evaluated by a veterinarian and the stool examined for *C. parvum*.

Human carriers of *Salmonella* species have been well documented. These people pose a risk to other persons. Therefore, known carriers should be treated for 4-6 weeks with ciprofloxacin, amoxicillin, norfloxacin, or trimethoprim-sulfamethoxazole. In addition, several vaccines are available for preventing *S. typhi* infection in humans. The mainstay of immunization for over a century has been the heat-killed, whole organism formulation that is considered to be over 80% protective. This vaccine consists of 2 doses given subcutaneously and requires a 4 week interval between doses. A booster is required every 3 years. Another vaccine uses the live, attenuated strain (Ty21a) of *S. typhi*. This vaccine is taken as an enteric-coated capsule ingested one hour before a meal every other day over a seven day period (i.e. a total of 4 doses). It is thought that the live, attenuated vaccine causes fewer adverse reactions than the heat-killed formulation. A newly licensed Vi capsular polysaccharide vaccine (ViCPS) has two major advantages over the other two vaccine products: few associated side effects and only one dose is required (25 µg of Vi in 0.5 ml given intramuscularly).
Regulations

By Wisconsin law, infections with *Campylobacter* species, *Yersinia* species, *Salmonella* species, *G. lamblia*, *C. parvum*, or *E. coli* O157:H7 in humans are considered Category II Reportable Diseases. Identification of a case or suspected case must be reported to the patient’s local health officer within 72 hours by submitting an Acute and Communicable Disease Case Report (DPH 4151) or by other means.

By Wisconsin law, *Salmonella* infections in sheep, goats and birds and *Campylobacter fetus* infection of cattle must be reported to the State Veterinarian within 10 days of diagnosis.
Selected References:


Definition of the Problem

Infections with influenza viruses that circulate within the human population are a common and important cause of respiratory disease in people regardless of their occupation, and cause an average of approximately 20,000 deaths and 114,000 hospitalizations/year in the United States alone. However, it is important to recognize that influenza viruses from pigs and potentially other animals can cross the species barrier to infect in-contact human beings in rural or animal occupational settings. Interestingly, a number of the recognized occurrences of zoonotic swine influenza have taken place here in Wisconsin. Documentation of zoonotic infections is important to an overall understanding of the epidemiology and ecology of influenza. In addition, given the role that pigs can play in genetic reassortment and adaptation of avian influenza viruses to replication in mammals, swine farmers, veterinarians and related personnel may serve as important sentinels for the emergence of novel influenza viruses from lower animal reservoirs. Thus, identification of zoonotic influenza virus infections is important for overall pandemic preparedness.

The Etiologic Agent. Influenza viruses are members of the Orthomyxoviridae family of viruses. Influenza A viruses (the most common type of influenza virus infecting both animals and people) contain 8 segments of RNA that encode 10 viral proteins. The two large surface proteins on the virus are the hemagglutinin (H or HA) and neuraminidase (N or NA). The HA contains the important antigenic sites to which protective antibodies are directed, and antigenic and genetic differences in the HA and NA define an influenza virus’ subtype, e.g., H1N1, H3N2 and so on. In total, there are currently 15 HA and 9 NA subtypes recognized among influenza A viruses. Infection or vaccination with a particular subtype generates little if any cross-protective immunity to the other subtypes.

Pathophysiology and Clinical Presentation

The basic Pathophysiology and Clinical Presentation of influenza in humans is well known and will not be outlined in detail here. As regards zoonotic swine influenza, examination of the cases to date suggests that there are no clinical findings that consistently help one to differentiate these infections from routine human influenza virus infections. Although the number of documented cases of zoonotic swine influenza are small, they have included both men and women across a wide range of ages. Of interest, however, is the fact that a number of zoonotic swine influenza virus infections have proven fatal for the people involved. It remains unclear whether this represents truly enhanced pathogenicity of swine influenza viruses compared to routine human influenza viruses in people, or whether this is simply an artifact of more complete characterization of viruses recovered from fatal infections. In some cases, fatal infections have occurred in patients with underlying health concerns, such as an immunocompromised child, a child with Hodgkin’s disease and a pregnant woman. However, other cases have occurred in individuals with no other apparent compromises to their health. In virtually all cases of zoonotic swine influenza, contact with pigs can be confirmed, but the level of contact has ranged from simply visiting a county fair to prolonged, direct, daily contact as an animal handler or farmer.
The occurrence of H5N1 and H9N2 virus infections among people in Asia in 1997-1999 highlighted the potential for avian influenza viruses to cross species barriers to infect humans. The H5N1 viruses were of particular concern because the case-fatality rate was 33% (6 of 18 infected people died). Fortunately, these viruses did not spread efficiently from person-to-person, and thus a population-wide antigenic shift and influenza pandemic did not occur. Direct avian-to-human transmission of influenza viruses such as these were rarely observed prior to 1997 and have not been documented in the United States. In large part, this is due to the fact that barriers to interspecies transmission of influenza viruses exist. The basis for this host-range restriction among influenza viruses has not been fully defined. It is considered to be a polygenic trait and evidence exists for contributions by multiple viral genes. However, the HA is thought to be a major host range factor since it is the receptor binding protein. Influenza viruses bind to sialic acid molecules to gain entrance to cells. Avian influenza viruses preferentially bind to cells using receptor molecules with an _2,3 linkage between sialic acid and galactose (present on intestinal epithelial cells in ducks, but largely lacking in the human respiratory tract), whereas human influenza viruses prefer receptors with a _2,6 sialic acid-galactose linkage (present on tracheal epithelial cells in humans, but lacking in the avian intestinal tract). As a consequence, human influenza viruses do not replicate efficiently in birds, and vice versa. In contrast, pigs are uniquely susceptible to infection with human and avian influenza viruses because their tracheal epithelial cells express both _2,3 and _2,6 receptors. As such, pigs have been hypothesized to be the “mixing vessel” hosts for human-avian virus reassortment events such as those that led to the 1957 and 1968 “Asian” and “Hong Kong” global influenza pandemics. In support of this theory, human-avian virus reassortants have been isolated from commercially-raised pigs in Europe and, thereafter, from children in the Netherlands.

### Agricultural Factors

Influenza viruses cause clinically important disease in a wide variety of animals. These include poultry, horses, pigs and even marine mammals. In mammals, infections present in a manner highly analogous to influenza in humans. In chickens and turkeys, however, influenza virus infections can present as a mild respiratory infection or as a multisystemic disease with edema and hemorrhages throughout many tissues, including the myocardium and CNS. The later form of disease is associated with genetically distinctive “highly pathogenic avian influenza viruses,” which are all H5 or H7 subtype viruses. Influenza virus infections in ducks and other waterfowl are subclinical. In these species, infection targets the gastrointestinal tract rather than the respiratory tract, with subsequent shedding of virus into the water they swim on. The subclinical nature of these infections, the fact that all 15 HA and 9 NA subtypes of influenza exist among waterfowl, the migratory behavior of waterfowl and the ability of influenza viruses to persist in cold lake water all contribute to the capacity of waterfowl to form an immense global reservoir for influenza viruses in nature. However, as discussed previously, influenza viruses rarely cross the species barrier directly from birds to humans. Likewise, equine influenza viruses are not considered to be of zoonotic concern.

The species of primary concern for zoonotic spread of influenza viruses is pigs. The histories of influenza in humans and in pigs are intimately related. Swine influenza was first recognized clinically in the Midwestern United States in 1918, contemporary with the devastating “Spanish flu” pandemic that killed 20-40 million people around the world. The first influenza viruses to be isolated in culture...
were recovered from pigs in 1930. These were the progenitors of the “classical” H1N1 lineage of swine influenza viruses, and recent research indicates that these viruses and the 1918 human influenza viruses were very closely related to each other and an avian progenitor virus. It remains unclear, however, whether the progenitor H1N1 virus first emerged in pigs and then spread to people, or vice versa. Since 1930, the classical H1N1 swine influenza viruses have circulated within the swine populations of many parts of the world, including North America, Europe and Asia.

Today, zoonotic infections may only be recognized if information regarding contact with sick pigs is specifically communicated to physicians, if a patient is hospitalized or dies, or if virus isolation is pursued and yields a virus that is antigenically atypical. In the vast majority of cases, however, swine influenza virus infections in people may not be clinically distinguishable from routine human influenza virus infections. As such, it is entirely possible, if not probable, that zoonotic swine virus infections occur more commonly among rural residents in contact with pigs. This is supported by the results of several serologic surveillance studies conducted in the 1960s, as well as a study completed here in Wisconsin in 1996-1997. In the later study, seropositivity to reference swine and human influenza viruses among 74 swine farm owners, employees, their family members and veterinarians in rural south-central Wisconsin was compared to seropositivity among 114 age-matched urban Milwaukee Wisconsin residents. The number of swine farm subjects with positive serum hemagglutination-inhibition (HI) antibody titers $\geq 40$ to swine influenza viruses (17/74) was significantly (p = 0.000002) higher than the number of seropositive urban control samples (1/114). Similarly, the geometric mean serum HI antibody titers to swine influenza viruses were significantly (p = 0.0001) higher for the farm subjects than the urban control subjects. Seropositivity to swine viruses among the farm subjects was significantly associated with being a farm owner or farm family member, living on a farm or going into the swine barn $\geq 4$ days/week. Overall, the results of this study suggest that people involved in swine farming are exposed to swine influenza viruses more commonly than the relatively small number of zoonotic swine influenza infections that are documented in the literature would suggest.

It should be pointed out that there have been substantial changes in the epidemiology of swine influenza in North America over the past several years that may ultimately have an impact on human influenza. Since 1997, novel viruses of 3 different subtypes and 5 different genotypes have emerged as agents of influenza among pigs in the United States and Canada. The appearance of these viruses is remarkable because there were no substantial changes in the overall epidemiology of swine influenza in North America for over 60 years prior to this time. Viruses of the classical H1N1 lineage were virtually the exclusive cause of swine influenza from the time of their initial isolation in 1930 through 1998. However, reassortant H3N2 viruses with genes derived from human, swine and avian viruses have become a major cause of swine influenza in North America since 1998. In addition, H1N2 viruses that resulted from reassortment between the triple reassortant H3N2 viruses and classical H1N1 swine viruses have been isolated subsequently from pigs in at least 6 states. Of particular note, an H1N1 virus that was also a reassortant between the triple reassortant viruses and classical H1N1 swine viruses was isolated from a man with swine contact in Wisconsin in 1998. This person developed typical influenza-like illness and recovered uneventfully after antiviral and supportive therapy. Finally, avian H4N6 viruses crossed the species barrier to infect pigs in Canada in 1999. Fortunately, these H4N6 viruses have not been isolated beyond their initial farm of origin. If these viruses spread more widely, they will represent another antigenic shift for our swine population, and could pose a threat to the
world’s human population, which is immunologically completely naïve to H4 subtype viruses.

Finally, an avian species in our region that may warrant greater attention is turkeys. This is because they are uniquely susceptible to infection with the classical swine H1N1 influenza viruses. The zoonotic risk from turkeys has not been well defined, but at least one instance of infection with a swine H1N1 virus from a turkey has been documented in a laboratory worker.

Management Issues for Human Health

**Diagnosis.** Influenza virus infection is most commonly diagnosed by identification of the virus in rapid antigen-capture kits or isolation of the virus in cell or egg culture from nose or throat swabs or pharyngeal gargle specimens. Samples should be placed into containers of viral transport medium and sent to the appropriate laboratory as quickly as possible. If immediate transportation is not possible, the samples should be kept on ice overnight.

If circulation of influenza virus is confirmed in a given region by a local health department, a clinical diagnosis may is considered acceptable (i.e. a patient presenting with fever, cough, and muscle aches during the winter). However, virus isolation should be aggressively pursued in cases where zoonotic infections are suspected.

Subtyping of the virus can be conducted by means of serologic assays (hemagglutination-inhibition and neuraminidase-inhibition) using subtype-specific reference antisera. Since only H1N1 and H3N2 viruses routinely circulate among human beings (although a number of H1N2 viruses were also isolated in 2001-2002), identification of a virus of any other subtype should create suspicion of a zoonotic infection. In those cases, or when conventional H1N1 or H3N2 viruses react abnormally in antigenic analyses, genetic sequencing and phylogenetic examinations can be conducted to determine the evolutionary origin of the virus. This level of documentation is no longer considered unusual and may be important to individual patient care, in public health inquiries for identification of potential additional cases of zoonotic infections, and for pandemic preparedness.

**Treatment.** Amantadine and rimantadine are oral medications that are effective in treating influenza A. Their mechanism of action is linked to their ability to inhibit fusion of the virus to the host cell (i.e. they prevent viral uncoating). Numerous studies have now shown that both of these antiviral drugs will decrease the duration of symptoms as well as reduce the levels and duration of viral shedding when compared to placebo. In order to be effective, however, both amantadine and rimantadine must be taken within 48 hours of symptom onset. Regardless of which drug is used, treatment of influenza A requires a dose of 100 mg twice daily for 5 days. However, the dose of both antiviral medications should be reduced to 100 mg per day in persons over the age of 65, persons known to have hepatic dysfunction, and persons with a creatinine clearance of less than 50 ml per minute. Because amantadine has been associated with frequent adverse drug reactions (i.e. nausea, anorexia, edema, anxiety, insomnia, etc.), rimantadine is the more commonly used agent.

Both of the new neuraminidase inhibitors, oseltamivir and zanamavir, have been approved by the U.S. Food and Drug Administration to treat influenza A and B. In order to decrease the severity and duration of illness, both neuraminidase inhibitors must be taken within 36 hours of symptom onset. Oseltamivir
is an oral medication that can also be used to treat rimantadine-resistant influenza A. For treatment of influenza, the dose of oseltamivir is 75 mg twice daily for 5 days. Zanamavir is an inhaled drug that may cause bronchospasm in certain individuals. For treatment of influenza, the dose of zanamavir is 2 inhalations (10 mg) twice daily for 5 days.

**Prevention.** The cornerstone of preventing influenza in humans is the widespread use of the inactivated vaccine that is prepared each year. This trivalent vaccine is effective against the common strains of both influenza A and influenza B virus. The vaccine should be administered in autumn to ensure that antibody levels rise to high levels prior to influenza season. Persons who are allergic to eggs should not receive the vaccine. In contrast, influenza vaccine is strongly recommended for any person over 6 months of age who is at increased risk for complications of influenza as well, as persons who care for these high-risk patients. Groups that the CDC targets for immunization include:

- persons 50 years of age or older
- residents of nursing homes and other chronic care facilities
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic disease (including diabetes), renal dysfunction, hemoglobinopathies, or immunosuppression
- children and teenagers who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye’s syndrome following influenza infection
- women who will be in the second or third trimester of pregnancy during influenza season
- physicians, nurses, and other personnel in both hospital and outpatient-care settings, including emergency response workers
- employees of nursing homes and chronic-care facilities who have contact with patients or residents
- employees of assisted living and other residences for persons in high-risk groups
- persons who provide home care to persons in high-risk groups
- household members, including children, of persons in high-risk groups.

Importantly, persons that work closely with pigs are not considered vaccine candidates solely on the basis of their occupation. The reason for this is that influenza strains circulating in pigs are not included in vaccine preparations that are commercially available each year.

Chemoprophylaxis with antiviral medications is also beneficial, particularly for persons who are not immunized against influenza. Antiviral medications also have a role in controlling local or regional outbreaks. Moreover, antiviral preventive therapy will undoubtedly play a role in the next influenza pandemic, since new strains created as a result of antigenic shift will hopefully remain susceptible to amantadine, rimantadine, zanamavir, and/or oseltamivir. Currently, all four of these antiviral medications are effective in preventing influenza in humans. Oseltamivir will prevent 87% of culture proven influenza at a dose of 75 mg daily. Zanamavir will prevent 67% of culture proven influenza and 84% of febrile influenza at a dose of 2 inhalations (10 mg) daily. A prospective randomized trial of over 1,000 nursing home residents in Wisconsin demonstrated the benefit of rimantadine at a dose of 100 mg daily. No residents developed influenza A after drug prophylaxis with rimantadine was
The duration of rimantadine chemoprophylaxis in this study was 14 days or 7 days without the onset of a new case, whichever was longer.

**Selected References**


Zoonotic tuberculosis due to infection of people with *Mycobacterium bovis* was historically one of the most important public health problems in the United States. However, this agent has been very nearly eradicated from the United States through the activities of a national veterinary control program that has been in place for many years. In light of this, tuberculosis will not be covered here in detail. However, zoonotic tuberculosis deserves a brief review because *M. bovis* has appeared in the wild and captive-raised deer populations of the northeastern portion of the southern peninsula of Michigan in the past several years. Along with this, there has also been limited spill-over into the domestic cattle population of Michigan and, in 1995, Wisconsin. The on-going presence of *M. bovis* in deer will continue to threaten our cattle population, with the potential (though remote) for human exposure. Therefore, the epidemiology of tuberculosis is briefly reviewed herein, with emphasis on differentiating *M. tuberculosis* from *M. bovis* and *M. avium-intracellulare*.

*Mycobacterium tuberculosis* is the classic agent of human tuberculosis. Humans are the reservoir for this species of *Mycobacterium*, although animals can be infected as a “reverse zoonosis” or “anthropozoonosis.” Infection of cattle with *M. tuberculosis* can complicate skin testing for *M. bovis*, but cattle generally do not become clinically sick following *M. tuberculosis* infection. Pigs were historically infected with *M. tuberculosis* by eating food scraps from the household of an infected person, leading to granulomas in the gastrointestinal tract and associated lymph nodes. Finally, dogs develop granulomas in various parts of the body and, if the organism is replicating in the pharynx, can transmit the organism back to other people.

*Mycobacterium bovis* is the organism responsible for classical bovine tuberculosis, and it was of great concern to humans as a zoonotic disease prior to the onset of pasteurization. It is still a concern in underdeveloped regions of the world where pasteurization is not practiced and where bovine tuberculosis has not been controlled. (It should be appreciated that some farm families even here in Wisconsin continue to drink unpasteurized milk obtained directly from their own animals.) As with *M. tuberculosis* in humans, *M. bovis* is spread from cow-to-cow by inhalation of the organism in aerosolized droplets. The pathology in cows is also similar to the pathology of *M. tuberculosis* in humans, with pulmonary tuberculosis leading to chronic debilitation and coughing, and the potential for systemic spread to other organs. Approximately 1-2% of *M. bovis* infected cows develop mycobacterial mastitis, with shedding of the organism in the milk. In goats, *M. bovis* presents in a manner similar to the disease in cattle. In contrast, infection in pigs usually occurs following ingestion of contaminated milk or contaminated cattle feed, leading to pathology in the gastrointestinal tract and associated lymph nodes. Likewise, *M. bovis* infection in sheep, horses, dogs and cats produces gastrointestinal and lymph node pathology, but infection is very rare in these species.

When humans are infected by ingestion of *M. bovis* in milk, the organism also most commonly localizes to the gastrointestinal tract and regional lymph nodes. This was the primary form of *M. bovis* tuberculosis in humans during the pre-pasteurization age. When humans are infected by inhalation of the organism (shed from the airways of infected cattle), they can develop classic pulmonary...
tuberculosis similar to that seen with *M. tuberculosis* infection. In addition, people can then shed the organism from their airways back to other cattle. However, person-to-person transmission of *M. bovis* is quite rare. As with *M. tuberculosis*, multidrug resistance is beginning to be detected in *M. bovis* strains, which creates a significant concern for HIV patients in developing countries.

The *M. avium-intracellulare* group of mycobacteria are widespread as infections in many species of birds, and the organisms can persist in soil and water. These organisms occasional infect domestic animals and humans, though the infections are almost always due to acquisition of the organism from the environment, not from direct contact with birds. *M. avium-intracellulare* is of significant concern as a cause of tuberculosis in immunocompromised patients. This is the cause of approximately 40% of the cases of disseminated tuberculosis in immunocompromised patients, and is of special concern because it is inherently resistant to anti-TB therapy. In birds, *M. avium-intracellulare* infections lead to granulomas in a variety of organ system (gastrointestinal, liver, spleen). In pigs, infection produces granulomas in the lymph nodes of the head and gastrointestinal tract. This is a relatively common infection of swine raised outdoors, with lesions detected at slaughter in 1-3% of such pigs. In cattle, *M. avium-intracellulare* infections are relatively uncommon and there is generally no detectable pathology, but infection can complicate skin test screening for *M. tuberculosis* and *M. bovis* infection.
Selected References


