

Rat Bite Fever

Streptobacillus moniliformis infection: Streptobacillary Fever, Epidemic Arthritic Erythema, Haverhill Fever, Streptobacillosis

Spirillum minus infection: Sodoku, Spirillary Fever

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Etiology

Rat-bite fever is caused by two bacterial species, *Streptobacillus moniliformis* and *Spirillum minus*. The two forms of the disease are known, respectively, as streptobacillary rat bite fever and spirillary rat bite fever. Haverhill fever is a form of *S. moniliformis* infection acquired by ingesting contaminated food or water.

In the U.S., rat bite fever is usually caused by *S. moniliformis*, a Gram negative pleomorphic bacillus. This organism has also been called *Streptothrix muris ratti*, *Nocardia muris*, *Actinomyces muris*, *Actinobacillus muris*, *Proactinomyces muris*, *Haverhillia multiformis*, and *Asterococcus muris*.

S. minus commonly causes rat bite fever in Asia. This organism is a short Gram negative spiral with two or three turns. Relatively little has been published about *S. minus*; it has never been cultivated in artificial media and is not well characterized.

Geographic Distribution

Streptobacillus moniliformis and *Spirillum minus* can be found worldwide; however, *S. minus* is common only in Asia. Human cases attributed to *S. minus* have also been reported in Africa.

Transmission

Streptobacillus moniliformis and *Spirillum minus* are part of the normal nasopharyngeal flora of rats, particularly wild rats. Other rodents, which contract these bacteria from rats, can also transmit rat bite fever. Infections caused by cats, dogs, ferrets, and weasels have been described in humans; these animals probably acquire the organism when they catch rodents. In most cases, *S. moniliformis* and *S. minus* are transmitted in bite wounds or scratches, but aerosol spread can also occur. Human infections with *S. moniliformis* have been reported after handling an animal, being exposed to its urine, or kissing it. Vertical transmission does not occur in rodents.

Haverhill fever, caused by *S. moniliformis*, is caused by eating or drinking food or water that has been contaminated with rat feces or urine.

Disinfection

S. moniliformis is susceptible to various disinfectants including 70% ethanol, 1% sodium hypochlorite, and 2% glutaraldehyde. It can also be inactivated by heating at 121°C for 15 minutes. This organism can survive in the environment for up to 10 days at 4°C.

S. minus has not been cultured in artificial media and its disinfectant susceptibility has not been established.

Infections in Humans

Incubation Period

The incubation period for streptobacillary rat bite fever is 2 days to 3 weeks. Most cases appear within 3 to 10 days.

The incubation period for spirillary rat bite fever ranges from 1 day to 6 weeks. Most cases appear in 14 to 18 days.

Clinical Signs

Streptobacillary rat bite fever

Wounds infected by *S. moniliformis* usually heal without inflammation, often before the first symptoms of rat bite fever appear. Rat bite fever usually begins abruptly with a fever and chills. Other common symptoms include severe myalgia and joint pain, headache, nausea, and vomiting. Many patients develop a maculopapular, purpuric, or petechial rash. This rash occurs most often on the extremities, particularly the hands and feet. Hemorrhagic pustules and papules may also be seen. Infants and young children can develop severe diarrhea, which may lead to weight loss.

Most cases of rat bite fever resolve spontaneously within two weeks. However, complications and deaths can occur in untreated cases. Approximately half of all patients with streptobacillary rat bite fever develop nonsuppurative polyarthritis, often within a week of the onset of symptoms. It may affect the knees, shoulders, elbows, wrists,

and hands, and it may be migratory. Arthritis can persist for months and up to two years, with periods of remission and exacerbation. Other serious complications including tenosynovitis, endocarditis, pericarditis, myocarditis, hepatitis, nephritis, meningitis, pneumonia, sepsis, and focal organ abscesses can also occur. Most deaths occur in infants and in patients who develop endocarditis. Fulminant, fatal sepsis has also been reported in previously healthy adults.

Spirillary rat bite fever

Spirillary rat bite fever is similar to streptobacillary rat bite fever. However, in this form of the disease, an indurated and often ulcerated lesion occurs at the site of the bite. This skin lesion may appear when the fever develops, if the wound initially healed without complications. Febrile relapses separated by afebrile periods are often seen in spirillary rat bite fever; these relapses can recur several times over 1 to 3 months. In addition, a distinctive rash consisting of large violaceous or reddish macules can occur. Erythematous plaques or urticaria may be seen in some patients. Arthritis is rare in spirillary rat bite fever; however, other serious complications resemble those seen in streptobacillary rat bite fever. Untreated infections can be fatal.

Haverhill fever

Haverhill fever is similar to streptobacillary rat bite fever, but it is accompanied by pharyngitis and pronounced vomiting. Complications including endocarditis, pneumonia, metastatic abscesses, and anemia may be seen in this form of the disease. Severe arthralgia and frequent relapses have also been reported.

Communicability

Person-to-person transmission has not been reported.

Diagnostic Tests

Streptobacillary rat bite fever

In humans, streptobacillary rat bite fever is usually diagnosed by culture of blood, joint fluid, or the wound. *Streptobacillus moniliformis* is a microaerophilic, Gram negative, pleomorphic bacillus. It often has spherical, oval, fusiform, or club-shaped swellings; in some cases, clumps of this bacterium may look like proteinaceous debris. Depending on the medium, it occurs singly or in chains. *S. moniliformis* is fastidious and must be grown in media with 20% serum, blood, or ascitic fluid; the laboratory should be informed that this organism is suspected, as it does not grow well on conventional media. Inoculation into rodents can also be used for diagnosis.

Serology is not considered to be reliable in humans. A slide agglutination test was formerly used in the U.S., but it is not longer available due to performance limitations.

Polymerase chain reaction (PCR) assays have occasionally been used in humans. In one case, PCR of blister fluid from the wound was positive when culture was unsuccessful.

Spirillary rat bite fever

Spirillary rat bite fever is usually diagnosed by identifying the organism in blood, lymph node aspirates, the bite wound, or erythematous plaques. *Spirillum minus* may be found in darkfield or phase contrast preparations, or after Giemsa, Wright's, or silver staining. This organism is a short, spiral-shaped, Gram-negative rod (0.2 to 0.5 μm by 3 to 5 μm) with two to three coils and bipolar tufts of flagella. It has not, to date, been successfully grown on artificial media. If microscopy is unsuccessful, blood or wound infiltrate can be inoculated into mice, guinea pigs or *S. minus*-free rats for diagnosis.

Treatment

Rat bite fever can be treated successfully with antibiotics. Penicillin is most often prescribed, but erythromycin, tetracycline, and other antibiotics are also used. Treatment results in a shorter clinical course and may prevent severe complications.

Prevention

The risk of infection can be reduced by avoiding exposure to rats, particularly wild rats. Wild rat populations around homes should be controlled; specific information on rodent control is available from the U.S. Centers for Disease Control and Prevention (CDC). Food and water storage should be designed to prevent contamination by rodents, and potentially contaminated water and food sources should be avoided. Pasteurization of milk and sterilization of drinking water decreases the risk of Haverhill fever.

Bites from rodents should be avoided as much as possible. Proper handling techniques and protective gloves can help prevent bites from laboratory animals. In addition, hand-to-mouth contact should be avoided with handling any rat or cleaning its cage. The hands should be washed after contact with rodents. If a bite occurs, it should be cleaned and disinfected promptly. In addition, the CDC recommends that persons bitten by a rat seek medical attention and report their exposure history to ensure that rat bite fever is considered in the differential diagnosis.

Morbidity and Mortality

Rat bite fever is not a reportable disease; however, it is thought to be rare in the U.S. As of 2004, only 200 cases had been reported. People who handle rats at home or at work, and children living in rat-infested areas are at an increased risk of infection. The incidence of rat bite fever seems to be increasing with the increasing popularity of rats as pets. Most cases are sporadic, but two large outbreaks of Haverhill fever have been reported: one in Haverhill, MA in 1926 and another in Essex, U.K. in 1983.

Up to 10% of rat bites may result in rat bite fever. Untreated *S. moniliformis* infections are fatal in approximately 10% to 13% of patients. The mortality rate for untreated spirillary rat bite fever is approximately 7% to 10%. Cases with endocarditis or pericarditis are more likely to be fatal; although these complications are rare, the mortality rate in these cases can be as high as 53%.

Infections in Animals

Species Affected

Rats are the reservoir hosts for both *Streptobacillus moniliformis* and *Spirillum minus*. *S. moniliformis* has also been found in mice, hamsters, gerbils, guinea pigs, squirrels, non-human primates, and birds, as well as in animals that eat rodents such as cats, dogs, ferrets, and weasels. Disease has been reported in mice, birds, guinea pigs, and non-human primates. *S. minus* also occurs in mice.

Incubation Period

The incubation period in experimentally infected guinea pigs is approximately 1 to 2 weeks.

Clinical Signs

Rats

Rats usually carry *S. moniliformis* and *S. minus* asymptotically. Occasionally, *S. moniliformis* occurs as a secondary invader in subcutaneous abscesses. It has also been reported from the middle ear of rats with otitis media, as well as from the middle ear of asymptomatic rats.

Other species

Symptomatic infections with *S. moniliformis* have been reported in a variety of species.

Infected mice may develop polyarthritis, subcutaneous and/or hepatic abscesses, various other purulent lesions, and acute or subacute septicemia. In epidemics of septicemia, some mice may be found dead. Others may be depressed and hunched for 1 to 2 days before death. Conjunctivitis, photophobia, cyanosis, diarrhea, anemia, hemoglobinuria, and emaciation may also be seen. Brown crusts can occur over the mammae of nursing females. Chronic arthritis, with swelling of the limbs or tail, may be a sequela. Deformation, ankylosis, or spontaneous amputation of the limbs or tail may occur. If the spinal column is involved, there may be posterior paralysis, kyphosis, and priapism. Abortions and stillbirths have also been reported. Some experimentally infected mice become bacteremic but remain asymptomatic.

S. moniliformis has also been associated with cases of granulomatous pneumonia or cervical lymphangitis in guinea pigs. Cervical lymphangitis is characterized by swelling and large abscesses in the cervical regional lymph nodes. In some experimentally infected guinea pigs, the first symptom is swelling and congestion of the inoculation site, accompanied by enlargement of the lymph nodes, fever, and weight loss. Some cases in guinea pigs are fatal.

Septic arthritis and endocarditis have been described in naturally infected nonhuman primates. Rhesus macaques experimentally infected with *S. moniliformis* can develop symptoms similar to human rat bite fever.

Symptomatic infections with this organism have also been reported in birds. Arthritis has been seen in naturally infected turkeys, and a tawny owl with infected feet was reported in the U.K.

Communicability

Rats can transmit *S. moniliformis* and *S. minus* in bites and scratches. Rat bite fever has also been seen in humans who were exposed to rat urine or feces, or who handled or kissed a rat. Human cases have also been associated with bites from other rodents and animals that eat rodents such as cats, dogs, and ferrets.

Diagnostic Tests

Streptobacillus moniliformis

Streptobacillary rat bite fever in animals can be diagnosed by isolation of the organism, serology, or molecular techniques.

Streptobacillus moniliformis is a microaerophilic, Gram negative, pleomorphic bacillus. It often has spherical, oval, fusiform, or club-shaped swellings; in some cases, clumps of this bacterium may look like proteinaceous debris. Depending on the medium, it occurs singly or in chains. *S. moniliformis* is fastidious and must be grown in media with 20% serum, blood, or ascitic fluid; the laboratory should be informed that this organism is suspected, as it does not grow well on conventional media. Inoculation into rodents can also be used for diagnosis.

Serologic tests including enzyme-linked immunosorbent assay (ELISA,) indirect immunofluorescence, and complement fixation can be used for screening in rodents. Polymerase chain reaction (PCR) assays are also used to detect genetic material.

Spirillum minus

Spirillary rat bite fever can be diagnosed by finding *Spirillum minus* in darkfield or phase contrast preparations, or after Giemsa, Wright's, or silver staining. *S. minus* is a short, spiral-shaped, Gram-negative rod (0.2 to 0.5 μm by 3 to 5 μm) with two to three coils and bipolar tufts of flagella. It has not, to date, been successfully grown on artificial media. If microscopy is unsuccessful, animal inoculation into rodents may be used.

Treatment

S. moniliformis and *S. minus* are susceptible to several antibiotics including penicillin, erythromycin, and tetracycline. Cervical abscesses in guinea pigs, as well as other abscesses, may require surgical removal or incision and drainage.

Prevention

Prevention depends on preventing contact between domesticated animals and wild rodents, particularly rats. Laboratory rats and mice can be cleared of infection by establishing cesarean derived, barrier maintained stocks. These animals should be monitored regularly for infections. Laboratory rats, mice, and guinea pigs should be kept in separate areas. To prevent them from becoming carriers of these organisms, cats, dogs, and ferrets should not be allowed to hunt wild rodents.

To reduce the incidence of cervical abscesses in guinea pigs, abrasive materials should not be used in feed or litter, and malocclusions and overgrown teeth should be corrected.

Morbidity and Mortality

S. moniliformis and *S. minus* are most commonly found in rats. An estimated 50% to 100% of wild rats carry *S. moniliformis* and up to 25% of the wild rats in some countries are thought to carry *S. minus*. At one time, *S. moniliformis* was also found in 10% to 100% of laboratory rats. However, with the advent of cesarean derived, barrier-maintained colonies, this organism has become rare in laboratory stocks. Nevertheless, a few outbreaks have been reported in cesarean-derived rodent colonies. *S. moniliformis* may still be found in some conventionally reared laboratory rats, and several recent cases in humans were associated with pet rats. Sporadic infections with *S. moniliformis* and *S. minus* have also been reported in other rodents, and epizootics of *S. moniliformis* septicemia have been seen in wild and laboratory mice.

The morbidity and mortality rates vary with the species. Rats infected with *Streptobacillus moniliformis* and *Spirillum minus* are usually asymptomatic. Infections in mice can be highly lethal; in some outbreaks, the morbidity and mortality rates approach 100%. High mortality rates have also been reported in experimentally infected guinea pigs. Cervical abscesses in guinea pigs are sometimes fatal.

Post-Mortem Lesions

In mice with acute septicemia, there may be few lesions. In subacute cases, the lesions may include multifocal, suppurative, embolic interstitial nephritis, as well as focal necrosis of the spleen and liver, splenomegaly, and lymphadenopathy. In mice that survive the acute disease, the predominant finding is septic polyarthritis characterized by numerous subcutaneous and periarticular abscesses. Fibrosis of the joints, joint deformation, and spontaneous amputation of the limbs and tails may be seen. Brown crusts, caused by severe, acute, diffuse neutrophilic dermatitis, may occur over the mammae of nursing mice with septicemia. Subcutaneous abscesses and liver abscesses have also been reported in some wild mice.

Cervical lymphangitis in guinea pigs is characterized by swelling, inflammation, and large abscesses in the cervical regional lymph nodes. Lesions can occur in other organs if the infection becomes disseminated.

Internet Resources

- Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/ncidod/dbmd/diseaseinfo/ratbitefever_g.htm#whatisrbf
- CDC Information on Wild Rodent Control
http://www.cdc.gov/ncidod/diseases/hanta/hps_stc/stc_spot.htm

Material Safety Data Sheets – Public Health Agency of Canada, Office of Laboratory Security
<http://www.phac-aspc.gc.ca/msds-ftss/index.html>

Medical Microbiology
<http://www.gsbs.utmb.edu/microbook>

The Merck Manual
<http://www.merck.com/pubs/mmanual/>

The Merck Veterinary Manual
<http://www.merckvetmanual.com/mvm/index.jsp>

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