Rat Bite Fever and *Streptobacillus moniliformis*

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INTRODUCTION

Disease following the bite of a rat has been known in India for over 2,300 years, but it has been described worldwide much more recently as rat bite fever. This term describes two similar yet distinct disease syndromes caused by *Streptobacillus moniliformis* or *Spirillum minus*. Rat bite fever caused by *S. moniliformis* is more common in North America, while *S. minus* infection, also known as sodoku, is more common in Asia. Streptobacillary rat bite fever, the subject of this review, is a systemic illness classically characterized by relapsing fever, rash, migratory polyarthralgias, and a mortality rate of 13% when untreated. Often associated with the bite of a wild or laboratory rat, rat bite fever historically has affected laboratory technicians and the poor. As rats have become popular as pets, this has changed such that children now account for over 50% of the cases in the United States, followed by laboratory personnel and pet shop employees. Over 200 cases of rat bite fever have been documented in the United States, but this is likely a significant under-representation because rat bite fever is not a reportable disease. Further, rat bite fever has a nonspecific presentation with a broad differential diagnosis, and isolation and identification of its causative organism, *S. moniliformis*, is not straightforward. Thus, the challenges of diagnosis and broadened demographic exposure demand close attention to this disease and its causative organism by clinicians.

HISTORICAL ASPECTS

Rat bite fever was first reported in the United States in 1839 (89). An association with a specific pathogen was not reported until 1914, when Schottmüller described *Streptothrix muris ratti*, isolated from a rat-bitten man (71). This association was confirmed in the United States in 1916 (9). In 1925, the organism
was renamed *Streptobacillus moniliformis* (48), a name that has remained in general use since, although some reports refer to *Actinomyces* or *Actinobacillus muris* (41, 87). A milk-associated outbreak of disease occurred in Haverhill, MA, in 1926 and was described by Place and Sutton (60). The organism found at this time was named *Haverhillia multiformis* by Parker and Hudson (55), although this most likely represents *S. moniliformis* disease. Any review of the literature regarding rat bite fever is complicated by the near-simultaneous description of *Spirillum minus*, the primary cause of rat bite fever in Asia, which is known by many as sodoku. Unfortunately, some reports discuss both organisms simultaneously, blurring the distinction between the two diseases and epidemiologic distributions that are, in fact, distinct.

**BIOLOGY**

**Morphology**

*Streptobacillus moniliformis* is a highly pleomorphic, filamentous, gram-negative, nonmotile, and non-acid-fast rod. It usually appears straight but may be fusiform and may develop tously, gram-negative, nonmotile, and non-acid-fast rod. It usually appears straight but may be fusiform and may develop tously, gram-negative, nonmotile, and non-acid-fast rod. It usually appears straight but may be fusiform and may develop tously, gram-negative, nonmotile, and non-acid-fast rod. It usually appears straight but may be fusiform and may develop tously, gram-negative, nonmotile, and non-acid-fast rod. It usually appears straight but may be fusiform and may develop...
reports come from the United Kingdom and France, but sporadic reports from Norway, Finland, Germany, Spain, Italy, Greece, Poland, Denmark, and The Netherlands also exist. Australia has also demonstrated some cases. Few reports from Africa exist, other than one report of sodoku from Kenya (8) and two episodes of squirrel bite-associated disease in Nigeria (33), probably underestimating the presence of *S. moniliformis*. Most reports from Asia document cases of sodoku, caused by *Spirillum minus* and not discussed here (91). Within the United States, most early reports originate from the eastern half of the country. However, *S. moniliformis* now appears to have migrated to the West Coast (13, 32), and cases are documented nationwide (34).

**Animal Infectivity**

**Rats.** The rat appears to be the dominant natural reservoir of *S. moniliformis*, which likely is a member of the commensal
flora of the rat’s upper respiratory tract. Healthy rats may demonstrate the organism in cultures of the nasopharynx, lar-
ynx, upper trachea, and middle ear (56). Healthy domesticated
or laboratory rats demonstrate S. moniliformis colonization
10% to 100% of the time, while wild rats appear to be 50% to
100% colonized (16). Most rats are asymptomatically colo-
nized but occasionally may demonstrate signs and symptoms of
disease.

Mice. Because mice are a preferred animal model for re-
search, a significant amount of effort has been expended to
identify their risk of colonization and disease from S. monili-
formis, as summarized by Wullenweber (91). It is well docu-
menced that laboratory mice may show symptoms of infection
with S. moniliformis, ranging from septic lymphadenitis to poly-
arthrit. However, it appears that not all strains of mice are equally susceptible to streptobacillosis and, in fact, many inbred strains demonstrate mild to no disease
whatsoever. This is important from a laboratory personnel
health risk perspective, as some animals may be asymptomatic
carriers with the potential to transmit disease via exposure to
saliva, as are rats. The persistence of S. moniliformis in mice is
deated in the literature and ranges from none (91) to 6 months
(70). Overall, there appears to be a low risk of rat bite fever
from the bite of a healthy, inbred laboratory mouse. However,
this may be different if the bite is by an outbred strain or wild mouse.

Other animals. There are reports of infection or colonization
in such potential pets as guinea pigs (44), gerbils (90), ferrets (31), cats (82, 91), and dogs (16, 57, 82). However, no
confirmatory evidence exists to prove the risk of transmission
from either cats or dogs. More likely, the latter two animals are
colonized only transiently after attacking or eating a rodent
colonized with S. moniliformis (57). Rat bite fever in nonhu-
man primates (rhesus macaque and titi monkey) has been
reported, and streptobacillary disease in turkeys and koalas has
been demonstrated (83).

### TABLE 1. Results of biochemical tests performed on the parent
strain and an L-phase variant of Streptobacillus moniliformis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Parent strain</th>
<th>L-phase variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidase</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Catalase</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Indole</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Nitrate</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Hydrogen sulfide</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Arginine hydrolysis</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Methyl red</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Phenylalanine deaminase</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Citrate</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Urea hydrolysis</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Esulin hydrolysis</td>
<td>Weak reaction</td>
<td>Weak reaction</td>
<td>Weak reaction</td>
</tr>
<tr>
<td>Glucose fermentation</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Galactose fermentation</td>
<td>Weak reaction</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Maltose fermentation</td>
<td>Weak reaction</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Mannose fermentation</td>
<td>Weak reaction</td>
<td>Weak reaction</td>
<td>Weak reaction</td>
</tr>
<tr>
<td>Other carbohydrates</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>TSI agar with serum (butt/slant)</td>
<td>Acid/acid</td>
<td>Acid/acid</td>
<td>Acid/acid</td>
</tr>
</tbody>
</table>

* Data are from references 17, 72, and 91.

### CLINICAL FEATURES

**Human Infectivity**

The reported incidence of rat bite fever caused by S. mo-
iliformis from laboratory rat bites is low. Of 65 cases of doc-
umented rat bite fever since 1938 that were reviewed for this
article, only 8 (12%) were attributed to a laboratory rat expo-
sure. This likely does not represent the true incidence of dis-
 ease in humans because of low clinical suspicion by clinicians
and the organism’s strict growth requirements. Similarly, the
incidence of wild-rat-associated disease is seriously underesti-
ated, as not all cases of rat bite fever are associated with an
actual bite. S. moniliformis may also be acquired by handling of
the animal or by exposure to its excreta or saliva. Nineteen of
the 65 reviewed cases (29%) documented no bite or known
exposure, consistent with literature reports that 30% of pa-
tients report no known bite (15, 32). However, as stated above,
10% to 100% of domestic rats and 50% to 100% of wild rats
carry S. moniliformis, and a known bite causes infection ap-
proximately 10% of the time. Thus, rat bite fever and rat
colonization with S. moniliformis represent a significant public
health threat that remains unrecognized.

**Rat bite fever is associated with three clinical syndromes in
the literature. Rat bite fever caused by S. moniliformis infec-
tion is the predominant form seen in the United States. Dis-
cease caused by Spirillum minus is known as sodoku and occurs
primarily in Asia. Ingestion of S. moniliformis via contaminated
food causes Haverhill fever, so named for the first description
of an outbreak in Haverhill, MA.**

**Initial Symptoms**

S. moniliformis-associated rat bite fever is a systemic illness
classically characterized by fever, rigors, and migratory poly-
arthralgias. After exposure, the incubation period ranges from
3 days to over 3 weeks but typically is less than 7 days. Many
patients report symptoms suggestive of an upper respiratory
tract infection during this time. If a bite has occurred, it typi-
cally heals quickly, with minimal residual inflammation and no
significant regional lymphadenopathy. Persistence of signifi-
cant induration at the bite site should suggest an alternate
diagnosis, including sodoku.

At disease onset, fevers begin abruptly and may range from
38.0°C to 41°C. Rigors associated with fevers are prominent.
Fever may resolve in 3 to 5 days but can relapse. Other fre-
quently reported symptoms in the initial phase of illness in-
clude headache, nausea, vomiting, sore throat, and severe my-
algias.

**Disease Progression**

As rat bite fever progresses, over 50% of patients develop
migratory polyarthralgias. The severity of pain and the pres-
ence of swelling and erythema indicate arthritis (38, 67, 80).
Reports also document the presence of synovitis and nonsup-
 purative arthritis suggestive of rheumatoid arthritis (40, 47,
67). The joints involved include both large and small joints of
the extremities. Many patients experience arthritis of at least
the knee and ankle during their illness. Migratory polyarthral-
gia is the most persistent finding of rat bite fever, lasting several years in some patients.

Nearly 75% of patients develop a rash that may appear maculopapular, petechial, or purpuric (20) (Fig. 2). Hemorrhagic vesicles may also develop on the peripheral extremities, especially the hands and feet, and are very tender to palpation (Fig. 3). Appearance of this rash, especially the hemorrhagic vesicles, in the setting of an otherwise nonspecific set of disease signs and symptoms should strongly suggest the diagnosis of rat bite fever. The rash may persist beyond the other, more acute, symptoms. Approximately 20% of rashes desquamate, especially those with hemorrhagic vesicles (20).

**Outcome**

Untreated, rat bite fever has a mortality rate of approximately 10%, ranging from 7% to 13% (15, 54, 65, 80, 91). Reported causes of death include endocarditis, refractory peri-
cardial effusion, bronchopneumonia, pneumonitis, periarteritis nodosa, volvulus, and overwhelming septicemia, with organisms found in both the adrenal glands and bone marrow at autopsy (14, 15, 62, 65, 72, 76). Although some patients appear to show spontaneous recovery from serologically confirmed disease (5, 13), a lack of effective antibiotic treatment is highly associated with death. Initiation of an appropriate antibiotic regimen usually precipitates rapid resolution of acute symptoms. However, some patients experience prolonged migratory polyarthralgias, fatigue, and slowly resolving rash.

**Review of English Literature**

**Epidemiology.** A review of the English language literature reveals 65 discrete case reports that provide full descriptions of the clinical presentation (2, 3, 5–7, 13–16, 18, 21, 22, 24–27, 29, 31, 33–36, 38–43, 45–47, 49–52, 54, 58, 61–65, 67–69, 77, 79, 80, 82, 84, 87, 90). Many additional cases are described within case series in which signs and symptoms specific to each case are not detailed (3, 54, 65, 69, 88). The 65 detailed cases were reported from 1938 to 2005 and primarily come from the United States,
although the United Kingdom, Europe, Canada, Australia, and Nigeria are also represented. The patient ages range from 2 months to 87 years. Fifty (77%) of the rat bite patients described were male. Twenty-six (40%) of the exposures occurred from a wild rat, 8 (12%) were from a laboratory rat, and 3 (5%) were from a pet shop rat. Twenty-two (34%) of the patients described a nonbite or nonrat exposure. The remaining cases occurred in association with bites from a ferret (one), mouse (one), squirrel (two), gerbil (one), and dog (one).

**Clinical findings.** Symptoms described include fever (92%), rash (61%), polyarthralgias (66%), myalgia (29%), nausea and vomiting (40%), headache (34%), and sore throat (17%). The mean temperature achieved during the cases was 39.4°C. Patients’ laboratory values reveal an average white blood cell count of 12,200 per cubic millimeter, with a polymorphonuclear cell and band form predominance. Only five patients demonstrated white blood cell counts higher than 15,000 per cubic millimeter. More significantly, the average erythrocyte sedimentation rate was 69 mm per hour. Only four patients had erythrocyte sedimentation rates below 15 mm per hour; these patients all had laboratory values obtained either very late in their clinical course or after recovery. Seven (10.8%) of the patients died, consistent with the published average mortality rate of 10%.

**Complications**

Published complications of rat bite fever include endocarditis, myocarditis, pericarditis, systemic vasculitis, polyarteritis nodosa, meningitis, hepatitis, nephritis, amnionitis, pneumonia, and focal abscesses (14, 24, 35, 54, 62, 78, 79, 83). Of these, endocarditis is the best described and carries the highest mortality rate (64). Seventeen patients with endocarditis associated with *S. moniliformis* infection have been described (14, 50, 58, 64, 68). A 1992 review of 16 of these patients (68) revealed that 8 of them had valvular disease prior to the onset of endocarditis, most commonly rheumatic heart disease. Most cases were defined by multiple positive blood cultures and had typical symptoms of rat bite fever accompanied by murmurs (100%), petechiae (13%), Osler’s nodes (13%), hepatosplenomegaly (33%), anemia (33%), and cardiac dysrhythmia (13%). Echocardiography was performed for four patients and demonstrated valvular vegetation in only two patients. The reported mortality rate associated with *S. moniliformis* endocarditis is 53% (68), and death may occur from 2 weeks to 3 years after symptom onset (58). However, a majority of these deaths occurred in the absence of effective antimicrobial therapy (14).

**Differential Diagnoses**

**Diseases.** The differential diagnosis of symptoms typical of rat bite fever (fever, rash, polyarthralgias) is extensive (27, 54, 63, 78). Possible bacterial causes include sepsis from such bacteria as *Streptococcus pyogenes* and *Staphylococcus aureus*, disseminated gonorrhea, meningococemia, *Sodoku* *S. moniliformis*-associated diseases (scarlet fever, rheumatic fever, poststreptococcal reactive arthritis), Lyme disease, ehrlichiosis, and brucellosis. Rickettsial infections, especially Rocky Mountain spotted fever, must be considered in areas where such infections are endemic. Such spirochetal infections as leptospiri-
extremities, and was mostly “rubelliform” in nature. The rash progressed over 3 days to include hemorrhagic lesions and lasted an average of 6 days. Polyarthritis was the most persistent symptom, lasting from 1 week to several months and severely limiting activity and weight bearing. Wrists and elbows were most frequently involved, followed, in order, by knees, shoulders, fingers, and ankles. Associated laboratory findings demonstrated an average white blood cell count of 11,500 per cubic millimeter, with 70% polymorphonuclear cells. Blood cultures in 11 of 17 cases and joint fluid aspirate cultures in 2 of 2 cases demonstrated an organism subsequently named *Havrhillia multiformis*, with characteristics identical to *S. moniliformis*. Outcomes were uniformly excellent, with no deaths and few permanent sequelae. Several patients, however, experienced chronic, recurring arthralgias.

**United Kingdom experience.** A second reported outbreak of Haverhill fever occurred in 1983 in 208 children at a boarding school in Chelmsford, Essex, United Kingdom (59). In a description of four cases from this outbreak (74), the clinical features were described as abrupt onset of fever with headache, peripheral erythematous rash, polyarthralgias, and subsequent sore throat. Initial diagnoses included viral illness (especially coxsackievirus), meningococcal septicemia, and erythema multiforme. The point source of the outbreak appeared to be raw milk, ingested by many students at the school. Students developed symptoms at school and were sent home to recover from an apparent viral epidemic, thus explaining the subsequent appearance of cases in London, Leeds, and Nottingham. Blood cultures from the four described patients demonstrated *S. moniliformis*, and the information was provided to health care workers caring for other students to assist with diagnosis and management.

**DIAGNOSIS**

**Culture**

Growth characteristics are discussed separately (see “Biology,” above).

**Fatty Acid Profiles**

Fatty acid profiles obtained by gas-liquid chromatography, together with characteristic growth, can be used for rapid identification of *S. moniliformis*. The major cellular fatty acid peaks are tetrdecanoic acid (14:0), palmitic acid (16:0), octadecanoic acid with linoleic acid (18:2) and oleic acid (18:1), and stearic acid (18:0) (66, 69). High-resolution polyacrylamide gel electrophoresis in conjunction with computer analysis has also been used to distinguish and confirm strains of *S. moniliformis* (19).

**Other Methods**

Serologic assays and slide hemagglutination tests, although used historically (12, 55, 70) and in some animal research (10, 91), are currently not available for use with humans. Although these assays are sufficiently sensitive, the increasing demand for rapid, more-sensitive tests likely has detracted from their utility. Molecular methods such as PCR show promise and have been used successfully with humans and laboratory animals (4, 7, 11, 43, 85). A PCR assay specific for *S. moniliformis* has been described by Boot et al. (11); it uses primers designed on the basis of 16S rRNA gene base sequence data of human and rodent strains of *S. moniliformis* (forward primer, 5′ GCT TAA CAC ATGCAA ATC TAT 3′; reverse primer, 5′ AGT AAG GCC CGT ATC TCA 3′). These primers showed 100% complementarity to *S. moniliformis* ATCC 14674T and *S. moniliformis* ANL 370-1. The PCR assay generated a 296-bp product which, when discriminated by BiaI restriction enzyme treatment, generated three fragments (128, 92, and 76 bp) specific to *S. moniliformis*. This assay has been used by others to examine both human- and animal-derived specimens and has been found to distinguish *S. moniliformis* from other organisms with great accuracy (4, 11, 85). However, until such an assay becomes more readily available, a diagnosis of *S. moniliformis*-associated rat bite fever requires a high clinical index of suspicion coupled with the appropriate use of culture and attention to ruling out alternate diagnoses.

**TREATMENT**

Penicillin is the treatment of choice for proven or highly suspected cases of rat bite fever. Tests of *S. moniliformis* antibiotic susceptibility by the disk diffusion method usually demonstrate sensitivity to penicillins, cephalosporins, carbapenems, aztreonam, clindamycin, erythromycin, nitrofurantoin, bacitracin, tetracycline, teicoplanin, and vancomycin; intermediate susceptibility to aminoglycosides, fluoroquinolones, and chloramphenicol; and resistance to trimethoprim-sulfamethoxazole, polymyxin B, and nalidixic acid (69, 91). Antibiotic susceptibility tests performed by broth macrodilution usually demonstrate the following MICs: penicillin, <0.03 μg/ml; cefalothin, <0.03 μg/ml; ceftriaxone, <0.03 μg/ml; vancomycin, 0.5 μg/ml; tetracycline, 0.25 μg/ml; erythromycin, 2 μg/ml; streptomycin, 8 μg/ml; and gentamicin, 1 μg/ml (68). Only one penicillin-resistant *S. moniliformis* strain has been demonstrated (81), and that was over 50 years ago.

Adults with rat bite fever should receive 400,000 to 600,000 IU/day (240 to 360 mg) of intravenous penicillin G for at least 7 days, but this dose should be increased to 1.2 million IU/day (720 mg) if no response is seen within 2 days (65). Children should receive 20,000 to 50,000 IU/kg of body weight/day (12 to 30 mg/kg/day) of intravenous penicillin G for 5 to 7 days, followed by 7 days of oral penicillin V, 25 to 50 mg/kg/day (maximum, 3 g/day) divided four times per day (27, 73). For penicillin-allergic patients, both streptomycin and tetracycline appear to be effective (61, 68), but erythromycin use has been associated with treatment failures (35). Cephalosporins have also been used successfully (16, 20) and may be considered if cross-allergenicity with penicillin is felt to be unlikely. Other antimicrobials may be considered, based on the in vitro susceptibility data presented above, but no published evaluations of their effectiveness exist.

Patients with *S. moniliformis* endocarditis require dual therapy with high-dose penicillin G in combination with streptomycin or gentamicin (50). The currently recommended dose for adults is 4.8 million IU/day (4.8 g) of intramuscular parenteral penicillin G if the isolate is susceptible to 0.1 μg/ml. If the isolate is more resistant, 20 million IU/day (12 g) of intravenous penicillin G should be used (65, 68) for adults. Children should receive 160,000 to 240,000 IU/kg/day (96 to 144 mg/kg/
day), up to the adult maximum of 20 million U/day (12 g) (68, 73). Successful treatment of adults with a 4-week regimen has been demonstrated (50). The appropriate treatment length for children is not known, although 6-week regimens generally are considered effective for other causes of bacterial endocarditis. The use of streptomycin appears to enhance activity against the cell wall-deficient L forms of S. moniliformis (68); one might anticipate that other aminoglycosides would provide the same benefit.

**CONCLUSIONS**

Rat bite fever, caused by S. moniliformis, is an under-recognized and under-reported disease characterized by abrupt onset of fever, rigors, and migratory polyarthralgias; it carries a mortality rate of approximately 10%. Although S. moniliformis is exquisitely susceptible to penicillin, most patients experience treatment delays due to the nonspecific nature of the clinical features, a broad differential diagnosis list, and difficulties in culture diagnosis. However, the changing epidemiology of rodent exposure, together with the risk of severe, invasive disease if left untreated, suggests that rat bite fever and S. moniliformis should occupy a more prominent place in our diagnostic thinking.

**REFERENCES**


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