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Review Article

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Streptobacillus moniliformis and rat-bite fever: rare or neglected zoonosis?

Abstract

Rat-bite fever, caused by *Streptobacillus moniliformis*, is often described as a rare zoonotic disease; however, due to underdiagnosis and the lack of epidemiological investigation, it is questioned whether it should be characterized as a neglected disease. Challenges in diagnosing *S. moniliformis* infections stem from the microorganism's demanding growth requirements and nonspecific clinical manifestations, which may lead to misinterpretations by healthcare professionals. Traditional culture methods are inefficient, whereas other diagnostic methods, such as PCR and mass spectrometry, offer greater accuracy but remain largely inaccessible in resource-limited settings. The lack of awareness of this zoonosis among human and veterinary health professionals further complicates early diagnosis and effective treatment. Although penicillin remains the first-line therapy, cases of antimicrobial resistance and treatment failures highlight the need for alternative therapeutic strategies. This review underscores the importance of systematic surveillance in animals and humans in urban and research settings, enhanced biosafety measures in animal facilities, and improved interdisciplinary collaboration between human and veterinary health sectors. Key recommendations include increased training for healthcare professionals, comprehensive epidemiological investigations, and structured surveillance protocols to better assess the disease. By addressing diagnostic limitations and improving prevention strategies, the impact of S. moniliformis on public health can be mitigated more effectively.

Keywords: laboratory animals, zoonosis, one health

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Introduction

Streptobacillus moniliformis is a Gram-negative bacterium of zoonotic interest due to its potential to cause severe symptoms in humans, despite reports in the literature classifying it as rare.[1,2] Belonging to the Leptotrichiaceae family, this bacterium is known for its association with rat-bite fever, a condition that can result in severe septic arthritis if not properly treated.[2–4] Research on *S. moniliformis* is limited due to its presumed low prevalence, adding complexity to the understanding of its epidemiology and pathogenesis. This bacterium is primarily transmitted by carrier rodents, especially rats, although other animals have also been implicated in the epidemiological chain.[5–7] Symptoms in humans and animals are varied and non-specific.[8,9] Accurate diagnosis of *S. moniliformis* is challenging due to its similarities with other bacterial infections.[1] Effective treatments generally involve broad-spectrum antibiotics, although the choice of medication may vary depending on the severity of the infection and the patient's response.[10] A comprehensive understanding of this pathogen is essential for a complete and rapid medical assessment, as cases continue to be reported in various parts of the world. The aim of this study is to compile literature data on the occurrence of cases involving the agent, as well as information on its biology, pathogenesis, diagnostic methods, and treatment. This information is intended to serve as a tool for human and veterinary health professionals, enabling them to identify potential cases and administer appropriate treatment to ensure the rapid resolution of the disease. Furthermore, although it is described in the literature as rare, this study also aims to promote a comprehensive diagnostic approach and in-depth epidemiological investigation to prevent it from being neglected.

Agent biology

S. moniliformis belongs to the class Fusobacteria, order Fusobacteriales, family *Leptotrichiaceae*, and genus *Streptobacillus*. It is a pleomorphic Gram-negative bacillus, also described as a coccobacillus,[2] non-motile, non-spore-forming, and non-encapsulated, with ends that may appear rounded and/or pointed, and capable of forming filaments.[11,12] It may present lateral bulbous swellings[12] and is found in chains.[1,11,13] The size of the bacilli can vary, ranging from 0.1 to 0.5 µm by 2.0 to 5.0 µm, and up to 10 to 15 µm, with chains that can reach 100 to 150 µm.[1,11] The organism can present in two forms: the bacillary form, which is typically found, and the L form, characterized by a deficiency in the cell wall, occurring either induced or spontaneously, growing with a "fried egg" colony morphology. The L form is described as non-pathogenic.[1,11,13,14] Typical colonies exhibit a "cotton ball" appearance in liquid media, while colonies grown on solid media appear circular, convex, grayish, smooth, and shiny. Some colonies may display the "fried egg" appearance observed in the L form after a few days of culture.[1] It is an extremely fastidious microorganism regarding growth conditions, requiring microaerophilia for development, which complicates its cultivation and isolation. Optimal growth requires enriched soybean tryptone agar or broth with 20% blood, serum, or ascitic fluid; however, the bacterium also grows on blood agar without causing hemolysis. *S. moniliformis* grows slowly, potentially taking up to 7 days.[1]

Animal infection

According to data in the literature, *S. moniliformis* can infect various animal species, playing a significant role in animal health, particularly in rodents, which are the primary natural reservoirs. Although many of these animals are asymptomatic carriers, the bacterium can have implications not only for the health of the rodents themselves but also for transmission to other animals and humans. Rodents, especially rats, are the main hosts of the microorganism, carrying the bacterium in their oral cavities and upper respiratory tract. Transmission among rodents can occur through direct contact, bites, secretions, or the ingestion of contaminated food and water. In addition to rats, other rodents such as mice, guinea pigs, and gerbils can also be

carriers, further increasing the zoonotic potential of the bacterium. In research facilities, breeding environments, and areas with infestations of synanthropic rodents, the presence of *S. moniliformis* can pose a significant public health risk, necessitating continuous monitoring and the implementation of preventive measures.[1,9,12,15]

Rodents

i. Rat (*Rattus norvegicus and Rattus rattus*)

Rats are considered natural reservoirs of the agent, which is part of the commensal flora of the upper respiratory tract of these animals.[1,9,13] It is estimated that between 50-100% of synanthropic rats carry the microorganism in their microbiota without showing symptoms.[16,17] For laboratory rats, similar percentages were observed until the emergence of animals with better sanitary quality, such as Specific Pathogen Free (SPF) animals.[16,18] Typically, these animals are asymptomatic, as described by Passaretti et al.,[17] but they may exhibit diseases such as pneumonia and otitis media.[17,19] *S. moniliformis* can be isolated from samples taken from the middle ear, nasopharynx, larynx, and trachea,[1,4,13,19] and is also present in the blood and urine of these animals.[20] The presence in urine is an important factor in the agent's potential for dissemination, as it can contaminate water and food. According to Gaastra et al.,[12] rats raised in conventional systems are natural hosts and asymptomatic carriers of the agent. This applies to the species *R. rattus* and *R. norvegicus*, which are kept as laboratory and pet rats.[12] Koppman et al.[21] isolated the microorganism from samples collected from the middle ear of 9 out of 16 Wistar rats raised in a conventional setting. The authors also observed that 15 animals tested positive for IgG in serological analysis, indicating that nearly all examined animals had come into contact with the agent.[21] According to Otto, Franklin, and Clifford,[20] in colonies where the agent is identified, all animals should be euthanized, not only due to the potential interference with research results in which these animals are used but also primarily because of its zoonotic potential.[20] Hayashimoto et al.[2] reported the isolation of the agent from a pet rat that died without known cause. A necropsy was performed for investigation, which revealed no significant changes. Samples were collected for culture and bacteriological isolation, as well as biochemical analyses, which yielded results compatible with *S. moniliformis*. Confirmation was achieved through PCR analysis, demonstrating high similarity to the expected profile for the agent.[2] DiGeronimo et al.[22] reported the infection of a female animal presenting with placentitis and dystocia, leading to euthanasia followed by necropsy and sample collection for culture, where the presence of Gram-negative filamentous rods was observed. The agent was confirmed by PCR.[22] Azimi et al.[23] published a study in which they assessed the presence of the agent in synanthropic rats by collecting blood samples for PCR analysis. They observed that 23% of the animals tested positive for the agent [23]. This percentage does not correspond to that reported by Wouters et al.[16] and Passaretti et al.,[17] which ranges from 50% to 100%. Passaretti et al.[17] also mention that the percentage in domestic rats can vary from 10% to 100%.[16,17] According to reports from the aforementioned authors, the microorganism has been isolated from domestic, synanthropic, and laboratory rats, as described in their studies. Moreover, periodic monitoring of animal health status is crucial to preventing the spread of the agent and its transmission to humans.[24,25]

ii. Mice (*Mus musculus*)

Mice can exhibit symptoms of infection such as weight loss, lymphadenitis, osteomyelitis, polyarthralgia, and abscesses, potentially progressing to septicemia and death.[1,13,19] Susceptibility may vary according to the strain, which is significant since some animals can be asymptomatic carriers with the potential to transmit the disease to humans, similar to rats.[1] It is important to note that mice are not considered natural hosts of *S. moniliformis*, which may explain the scarcity of reports of human disease following bites from these rodents. Pregnant females infected by the agent may experience interrupted gestation and abortion. Other important characteristics of infection in mice include reduced mobility and reproductive capacity due to arthralgia. Chronic infection can last for six months.[12] Wullenweber et al.[26] reported an outbreak in an animal breeding facility where SPF mice of various strains were produced. According to the authors, only animals of the C57BL/6J strain exhibited symptoms, and 825 animals (approximately 36% of the total in the facility) either died or had to be euthanized due to the severity of the symptoms, indicating a higher sensitivity of this strain to the agent. Treatment with ampicillin and chlortetracycline resulted in clinical improvement. However, euthanasia of all animals and a sanitation break were necessary to prevent contamination of other strains maintained in the same facility. The authors isolated the agent and tested the sensitivity in other strains through oral inoculation, observing that BALB/cJ, C3H/He, DBA/2J, CB6F1, and B6D2F1 mice were unaffected, except for two DBA/2J and B6D2F1 animals that showed seroconversion. Intravenous inoculation was also tested in C57BL/6J, DBA/2J, and BALB/cJ strains, with all animals testing positive in the indirect immunofluorescence assay, indicating seroconversion.[26]

Glastonbury, Morton and Matthews[27] reported an infection in a colony of Swiss mice maintained for producing serum used as a diagnostic reagent. The animals exhibited an antalgic position (curved and depressed), weight loss, and soft feces. Approximately 2-5% of the affected animals showed conjunctivitis and subcutaneous swelling in the joints. All symptomatic animals died within 1-2 days. Bacteriological culture and biochemical screening confirmed the presence of the agent.[27] This report highlighted the increased sensitivity of this strain to the agent, as was also noted by Wullenweber et al.[26] for the C57BL/6J strain.[26,27] Fornefett et al.[28] also evaluated the susceptibility of BALB/c and C57BL/6 strains to *S. moniliformis*. They performed intranasal inoculation of the agent and indirect contact of sentinel animals with bedding used by contaminated animals. Supporting the observations of Wullenweber et al.,[26] the authors demonstrated that the C57BL/6 strain showed greater sensitivity to the agent, with a 75% mortality rate. BALB/c animals did not show clinical signs of disease.[26,28] Taylor et al.[29] reported cases of polyarthritis in synanthropic mice caused by *S. moniliformis*. The animals were captured on a farm using traps, and symptoms such as swelling in the joints, abscesses, and polyarthritis were observed. After necropsy and collection of samples for bacteriological culture and isolation, results compatible with the agent were found.[29] According to reports from the aforementioned authors, and similar to observations in rats, the microorganism has been isolated from laboratory and synanthropic mice, as described in their studies. Moreover, periodic monitoring of animal health status is crucial to preventing the spread of the agent and its transmission to humans.[25]

iii. Guinea pig (*Cavia porcellus*)

It is noted that guinea pigs are susceptible to infection by *S. moniliformis*.[12] Aldred, Hill, and Young[30] reported the isolation of the agent in these animals during an outbreak in a colony, where the primary symptom was cervical adenitis. Initially, the authors attempted to isolate the agent using bacterial culture techniques designed for samples collected from rats and mice, but without success.[30] Following the recommendations of Smith,[31] they confirmed that the isolate from guinea pigs did not adhere to the same culture patterns as those from rats and mice regarding anaerobic conditions.[30,31] Kirchner, Lake,

and Wightman[32] also reported an infection by the agent that resulted in granulomatous bronchopneumonia in this species.[32] Boot et al.[33] described the resistance of guinea pigs to infection by *S. moniliformis* in their study. The authors used a strain of the microorganism isolated from a rat and inoculated it into experimental groups via oral and nasal routes. Over the weeks following inoculation, the animals were euthanized, and necropsies were performed along with the collection of samples for bacteriological, serological, molecular, and histopathological analyses. Based on the results, the authors observed the resistance of these rodents to infection by the agent.[33] The conclusion reached by the authors aligns with the reports observed for these rodents compared to the greater severity in rats and mice. Bemis et al.[34] reported a series of cases involving abscesses in guinea pigs, where a single bacterial agent was isolated following the addition of serum to the culture medium. Microscopic examination of clinical samples and cultures revealed rods with occasional small bulbous forms and long, wavy filaments. Based on these findings, the agent was identified.[34] As with rats and mice, periodic health monitoring is recommended.[25]

iv. Gerbil (*Meriones unguiculatus*)

The use of gerbils in scientific research is uncommon, as is their use as pets. Consequently, there is a lack of reports and recommendations regarding the sanitary monitoring of pathogenic agents in this species compared to other rodents.[25] Wilkins et al.[6] reported the isolation of the agent in a 39-year-old patient who bred gerbils and developed symptoms ten days after being bitten. Following bacteriological culture, isolation, and biochemical testing, *S. moniliformis* was identified.[6] Due to the fact that many scientific studies worldwide still rely predominantly on rodents, rigorous monitoring of these animals is essential, considering that they can act as asymptomatic carriers of the microorganism and may infect animal facility staff and individuals involved in research. Although there are no recent global data on the number of animals used in research, the potential risk posed by these animals can be observed in the study conducted by Sauer, Spielmann, and Rusche,[35] which demonstrated that in the European Union in 2002, a total of 10,731,020 experimental animals was reported, the majority of which were mice and rats.[35] Another study published by Frías-Álvarez and Ortiz-Millán[36] showed that in Mexico, from 2015 to 2021, the most commonly used species in scientific research were mice, rats, and guinea pigs.[36] Similarly, a report recently published by the Brazilian government in 2024 revealed the number of animals used in research in the country between 2019 and 2023, with rodents among the most frequently utilized species.[37] The maintenance of research colonies requires strict sanitary monitoring, including periodic microbiological testing and the implementation of quarantine measures for new animals. Additionally, the possibility of transmission to researchers and technicians who handle these animals must be considered, reinforcing the need for specific protocols to minimize occupational exposure to the pathogen. The recommendations of the Federation of European Laboratory Animal Science Associations (FELASA) include the implementation of differentiated sanitary monitoring programs for various rodent species, with periodic testing for *S. moniliformis* to ensure the safety of both the animals and the professionals involved in research. In the case of *S. moniliformis*, FELASA recommends annual monitoring of the pathogen in mice, rats, and guinea pigs, with no specific recommendations for other rodent species.[25] Matthews and Ausman[38] mentioned that the increasing number of pet rats and the use of rodents in research are factors contributing to the occurrence of the disease.[38] Given the risk of transmission between animals and humans, implementing biosafety measures in animal facilities and research centers to reduce handlers' exposure to the pathogen is of paramount importance. The use of personal protective equipment and strict hygiene protocols are commonly adopted measures to prevent potential contamination.

Other animals

Some authors mention that *S. moniliformis* infection can also be contracted through the bite of animals that have had contact with rats, either by feeding on them or by biting them.[8,12,17,39] Dogs and cats are included in this group, although they are supposedly rare transmitters of the disease to humans.[12,15]

v. Dog (*Canis lupus familiaris*)

There is a scarcity of reports in the literature regarding the isolation of *S. moniliformis* in dogs. Some studies link the disease in humans to infections that may be associated with contact with animals that had some form of contact with carrier rodents.[16,40] Ditchfield, Lord, and McKay[41] reported the case of a dog presenting symptoms such as vomiting, diarrhea, anorexia, polydipsia, arthralgia, and petechiae in the interdigital spaces. Blood samples were collected for bacteriological culture, and pleomorphic Gram-negative bacilli were observed. The animal was treated with chloramphenicol and penicillin, but unfortunately, it did not survive. There was no report of direct contact with rodents, but the animal had a habit of ingesting food found in the garbage, and this occurred the day before the onset of symptoms, suggesting that the ingested food could have been contaminated with secretions from carrier synanthropic rodents.[41] Wouters et al.[16] published a study in which they evaluated 18 dogs that had contact with synanthropic rats using oral swab samples. The samples were analyzed using the polymerase chain reaction (PCR) technique, with ten samples testing positive for *S. moniliformis*. These results demonstrated the possibility that dogs can become infected through contact with carrier rodents and, consequently, become sources of contamination for humans.[16]

vi. Cat (*Felis catus*)

Eisenberg et al.[42] published a study reporting the isolation of *Streptobacillus* sp. from a sample collected from a domestic feline with pneumonia. The animal was found dead on a dairy farm and subjected to a necropsy, during which changes suggestive of pneumonia were observed, later confirmed by histopathological analysis of the collected samples. In the bacteriological culture, Gram-negative bacilli were observed, and biochemical tests suggested results indicative of *S. moniliformis*. The authors performed confirmatory analyses using mass spectrometry, which showed differences between the isolated microorganism and reference samples of the agent but confirmed similarity with the *Streptobacillus* genus. Additionally, 16S rRNA sequencing was conducted, revealing a 98% homology with the reference strain of the agent.[42] Although the primary transmission route of *S. moniliformis* is associated with rodents, dogs and cats that come into contact with these animals can become carriers and spread the pathogen. Due to the close interaction between these pets and humans, the zoonotic risk should be considered, especially in domestic environments. Reported cases suggest that this closer contact with dogs and cats previously exposed to infected rodents may serve as a transmission route for humans. Therefore, it is essential to implement preventive measures, such as regular veterinary check-ups for pathogen detection and restricting domestic animals' contact with synanthropic rodents. Additionally, it is crucial that professionals working with dogs and cats in veterinary clinics, hospitals, or shelters are trained to recognize clinical signs consistent with the disease and to adopt appropriate biosafety protocols. Regular monitoring of

the pathogen should also be incorporated into the clinical routine, particularly for animals with a higher likelihood of exposure to rodents.

Human infection

The most well-known form of transmission of *S. moniliformis* to humans occurs through rat bites, but it is also known that transmission can occur through the bites of other carrier animals,[5–7] as well as through contact with secretions from carrier animals, which includes the ingestion of contaminated food and contact with contaminated fomites.[3,4,12,20] According to the literature, the risk of infection through bites from carrier animals ranges between 1-10%.[1,12,43] Two diseases have been described involving the agent: Rat-bite fever and Haverhill fever,[12,21] although they could be more accurately described simply as *S. moniliformis* infection, given that cases of rat-bite fever have been reported in the literature without a history of a bite.[11,45,55,67]

i. Rat-bite fever (RBF)

Rat-bite fever is described as a rare disease due to the low reporting of cases and is caused by the microorganism *S. moniliformis*. This condition can also be caused by another pathogen, *Spirillum minus*, which is more common in Asia.[1,4,8,12,15] It is primarily transmitted to humans through bites from infected rats but can also occur through bites from other animal species, classifying it as a zoonosis. Transmission can also occur through direct and/or indirect contact with secretions from these animals.[8,12,42] According to the literature, the risk of infection from rodent bites ranges between 2-10%.[44] The history of rat-bite fever dates back to the 20th century when it was first described as a disease transmitted by urban rats, but it has been known for over 2,000 years in India.[1,12] Although it is considered an uncommon condition, sporadic cases are still reported in various parts of the world, especially in areas with an abundant presence of synanthropic rodents. Rodents used as research models and kept as pets can also transmit the agent,[1] which is why sanitary monitoring of these animals should be conducted periodically. Early surveillance and diagnosis are essential, as the disease can easily be mistaken for other febrile illnesses.[8] The symptoms are quite nonspecific and include fever, vomiting, headache, skin rashes, abscesses, arthralgia, myalgia, and in more severe cases, the condition may progress to pericarditis, endocarditis, meningitis, septicemia, and even death.[1,4,8,9,10,16] The mortality rate is around 7-15% without adequate treatment.[1,8,45,46,47]

ii. Haverhill fever

Haverhill fever is associated with the consumption of food and/or water contaminated by secretions from carrier rodents.[3,12,48] The first report in the literature linked an outbreak of the disease to the consumption of milk contaminated with *S. moniliformis*. The disease received its name from this report, which occurred in 1926 in Haverhill, USA.[1,49,50] At that time, the disease, which affected 86 people, was associated with a microorganism called *Haverhillia multiformis*, later shown to be highly similar to *S. moniliformis*. Patients affected by Haverhill fever develop symptoms very similar to rat-bite fever; however, the absence of contact with rats led to the diagnosis of Haverhill fever.[1,12] Place and Sutton[50] reported a similar outbreak, also in the United States, involving 400 people, 92% of whom had received milk from the same source, suggesting that this was the contamination source.[50] Based on these reports, infections in humans caused by the ingestion of water and food contaminated by the microorganism have been described as Haverhill fever.[12] The scientific literature includes studies reporting cases related to these diseases, as shown in Table S1. This study compiled information from these reports regarding the individuals involved (age and sex), observed symptoms, transmission mechanisms, diagnostic methods, and treatment. These data are essential to assist healthcare professionals in identifying potential infection cases, raising awareness of this possibility, as most symptoms, as previously mentioned, are highly nonspecific. Studies have reported cases of rat-bite fever without a history of bites, highlighting the need for deeper epidemiological investigations to fully elucidate the origin of the infection. Among the 43 analyzed studies reporting infections caused by the agent, 19 (44%) were associated with bites; 11 (26%) had no history of bites but had contact with rodents; five (12%) had no history of bites but were in rodent-infested environments; four (9%) had no history of bites but had ingested possibly contaminated food or water; two (5%) had no history of bites but reported contact with a dog and/or cat; one (2%) had no history of bites but sustained a lesion while handling a cage housing a rodent; and one (2%) lacked available information.

Table S1 Studies containing reports of cases of infection by *S. moniliformis* in humans, including information about the patients, transmission mechanisms, diagnostic methods, and treatments used

Study	Patient (age/sex)	Symptons	Transmission	Diagnostic methods	Treatment
Hamburger M, and HC Knowles.[51]	54y/M	Hyperthermia, chills, headache, nausea, vomiting, rash.	Rat bite.	Bacteriological culture.	Chloramphenicol, penicillin G.
Lambe DW, et al.[52]	44y/M	Chills, hyperthermia, nausea, vomiting, generalized pain.	There is no history of bites, but rat infestation.	Bacteriological culture	Cephalothin, tetracycline.
Shanson DC, et al.[53]	Outbreak (children)	Hyperthermia, rash, arthralgia and sore throat.	Ingestion of contaminated raw milk.	Bacteriological culture and biochemical tests.	Penicillin, co-trimoxazole and tetracycline.
Mcevoy MB, et al.[54]	Outbreak	Hyperthermia, rash and arthralgia.	Ingestion of contaminated raw milk and water.	Bacteriological culture.	Erythromycin.
Wilkins, EG, et al.[6]	39y/M	Hyperthermia, rigors, sore throat, rash, and arthralgia.	Gerbil bite.	Bacteriological culture and biochemical tests.	Penicillin.
Peel MM.[7]	50y/M	Hyperthermia, cellulitis, and lymphadenopathy.	Dog bite.	Bacteriological culture and biochemical tests.	There is no information.

Table S1 Continued...

Frans J, et al.[39]	16y/M	Headache, vomiting, and hyperthermia.	Rat bite.	Bacteriological culture and biochemical tests; GasChromatoGraphical analysis of fatty-acid profiles.	Amoxicillin-clavulanate.
Torres L, et al.[55]	87y/M	Anorexia, polyuria, dysuria, slight dehydratation, weight loss, and hyperthermia.	There is no history of bite, but contact with dog and cat.	Bacteriological culture and biochemical tests; ChromatoGraphical analysis of fatty-acid profiles.	Levofloxacin.
Wallet F, et al.[56]	56y/F	Joint pain and swelling.	Rat bite.	Bacteriological culture and biochemical tests; gene sequencing.	Penicillin G, ofloxacin, rifampicin, and clindamycin.
Andre JM, et al.[45]	7y/M	Hyperthermia, maculopapular rash on the hands and feet, blisters on the face and elbows, and severe bilateral arthralgia.	There is no history of bite, but contact with rat.	Bacteriological culture; PCR.	Erythromycin and amoxicillin.
Clarke AM, et al.[57]	65y/F	Malaise, intermittent hyperthermia, arthralgia, rash and vomiting.	Rat bite.	Bacteriological culture and biochemical tests.	Benzylpenicillin.
Abdulaziz H, et al.[58]	68y/M; 30y/M	Joint pain and swelling and rash, especially in the hind limbs.	Ingestion of raw milk and rat infestation.	Bacteriological culture.	Ceftriaxone and penicillin G.
Albedwawi S, et al.[59]	14y/M	Hyperthermia, arthralgia, and rash.	There is no history of bite, but contact with rat.	Bacteriological culture.	Penicillin.
Dendle C, et al.[60]	49y/M	Hyperthermia arthralgia, myalgia, erythema, rash, and fatigue.	Rat bite.	Bacteriological culture and biochemical tests; gene sequencing.	Doxycicline.
Irvine LE, and TS Wills.[11]	60y/M	Hyperthermia, headache, generalized lymphadenopathy, pustular lesions on hands.	There is no history of bites, but contact with mice.	Bacteriological culture.	Ceftazidime, gentamicin, and penicillin.
Mignard S, et al.[61]	49y/M	Hyperthermia, chills, arthralgia, rash, and weight loss.	Rat bite.	Bacteriological culture; gene sequencing.	Amoxicillin-clavulanic acid.
Wang TKF, and SSY Wong.[62]	58y/F	Hyperthermia and arthralgia.	Rat bite.	Bacteriological culture and biochemical tests.	Ampicillin.
Nakagomi D, et al.[63]	74y/F	Arthralgia, myalgia, fatigue rash, and hyperthermia.	Rat bite.	Bacteriological culture; PCR.	Minocycline hydrochloride, and piperacillin sodium.
Trigo DM, et al.[64]	24y/None	Hyperthermia, vomiting, headache, myalgia, arthralgia, and macular lesions.	Rat bite.	Bacteriological culture and biochemical tests.	Penicillin, doxycicline and gentamicin.
Addidle M, et al.[65]	58y/M	Right-sided flank pain, hyperthermia, and lower limb weakness	There is no history of a bite, but contact with dog.	Bacteriological culture and biochemical tests; PCR.	Flucloxacillin, ceftriaxone, and rofloxacin.
Danion F, et al.[66]	41y/F	Intermittent hyperthermia, pustules, papules, and arthralgia.	Rat bite.	Bacteriological culture; gene sequencing.	Amoxicillin.
Mackey JR, et al.[67]	3y/M	Hyperthermia, irritability, lack of appetite, vomiting, pain when moving, and rash.	There is no history of a bite, but a wound from handling a pet rat's cage.	Bacteriological culture; PCR; and electrospray ionization followed by mass spectrometry (PCR/ESI-MS).	Ampicillin and amoxicillin.
Brown CM, et al.[68]	17y/F	Intermittent fever, nausea, vomiting, pain, and rash.	There is no history of bite, but contact with rat.	Bacteriological culture.	Ceftriaxone.
Okamori S, et al.[69]	79y/M	Hyperthermia, diarrhea, fatigue, and joint pain.	There is no history of bites, but rat infestation.	Bacteriological culture; gene sequencing.	Meropenem.
Regnath T, et al.[70]	48y/M; 66y/M	Hyperthermia, pain, and chills.	There is no history of bite.	Bacteriological culture; mass spectrometry.	There is no information.

Table S1 Continued...

Sato R, et al.[71]	52y/M	Hyperthermia, rash, nausea, vomiting, shortness of breath, acute arthralgia, and back pain.	There is no history of bites, but rat infestation.	Bacteriological culture; Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS); and PCR.	Ceftriaxone and penicillin G.
Kawakami Y, et al.[72]	71y/M	Hyperthermia and polyarthralgia.	There is no history of bites, but rat infestation.	Bacteriological culture; PCR.	Ceftriaxone, azithromycin, levofloxacin, and amoxicillin.
Vetter NM, et al.[73]	8y/F	Lethargy, relapsing hyperthermia, rash, and arthralgia.	There is no history of bite, but contact with rat.	Bacteriological culture.	Doxycycline.
Hammer A, et al.[74]	40y/M	Diffuse abdominal pain, paresthesia, and hypesthesia distal to dermatome T-10.	Rat bite.	Bacteriological culture and biochemical tests; PCR; and Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).	Ceftriaxone, metronidazole, and penicillin.
Hayakawa Y, et al.[75]	45y/M	Fatigue, arthralgia, hyperthermia, rush, and diarrhea.	Rat bite.	Bacteriological culture; PCR.	Piperacillin-tazobactam, ampicillin-sulbactam, vancomycin, and minocycline.
Suzuki K, et al.[76]	39y/M	Hyperthermia, headache, arthralgia, and joint stiffness.	Rat bite.	Bacteriological culture; Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).	Doxycycline, ceftriaxone, and amoxicillin.
Zamora LMJ, et al.[77]	66y/M	Intermittent hyperthermia, malaise, and arthralgia.	Ingestion of contaminated water and rat infestation.	Bacteriological culture and biochemical tests.	Ceftriaxone, amikacin, levofloxacin, tigecycline, penicillin G, and doxycycline.
Nelson C, et al.[78]	33y/F	Hyperthermia, arthralgia, myalgias, dyspnea, orthopnea, and palpitations.	There is no history of bite, but contact with rat.	Bacteriological culture; Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF); PCR	Ceftriaxone.
Torres Miranda D, et al.[47]	52y/F	Joint pain and swelling, weakness, confusion, and hyperthermia.	There is no history of bites, but rat infestation.	Bacteriological culture; Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS); gene sequencing	Vancomycin, piperacillin-tazobactam, and ceftriaxone.
Berbel D, et al.[79]	31y/M	Hyperthermia, unspecific cutaneous lesions in some fingers and feet, arthralgia, and rash.	There is no history of bite, but contact with rat.	Bacteriological culture; Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-ToF MS); PCR	Ceftriaxone.
Zhang WW, et al.[80]	54y/M	Hyperthermia, malaise, fatigue, chills, diarrhea, myalgia, skin rashes, pustules, petechiae, and jaundice.	Rat bite.	Bacteriological culture; metagenomic next-generation sequencing (mNGS); PCR	Tazobactam, piperacillin, doxycycline, and penicillin.
Grugan DB, et al.[81]	51y/M	Polyarthralgia, myalgias, hyperthermia, rigors, and rash.	Rat bite.	Bacteriological culture.	Amoxicillin-clavulanic acid.
Kämmerer T, et al.[8]	55y/F	Hyperthermia, hand and foot injuries, and arthralgia.	There is no history of bite, but contact with rat.	Bacteriological culture; Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-ToF MS)	Cefuroxime and penicillin G.
Matthews C, and S Ausman.[38]	35y/M	Nausea, vomiting, hyperthermia, chills, black stools, edema, rash on hands and feet, and arthralgia.	There is no history of bite, but contact with rat.	Bacteriological culture and biochemical tests	Ceftriaxone.

Table S1 Continued...

Roussel SC, et al.[82]	64y/M	Confusion, left hemiparesis, and multiple crusting lesions on the right side of the forehead.	Rat bite.	Bacteriological culture; Matrix-assisted laser desorption/ ionization time-of-flight mass spectrometry (MALDI-ToF MS); gene sequencing.	Amoxicillin.
Wallemacq S, et al.[83]	91y/M	Hyperthermia, delirium, asthenia, and arthralgia.	Rat bite	Bacteriological culture; Matrix-assisted laser desorption/ionization time-of-flight (MALDI-ToF).	Ampicillin, amoxicillin, and doxycycline.
Hall CW, et al.[84]	56y/F	Hyperthermia, headache, Polyarthralgia, paraesthesia, hyperreflexia, and weakness.	There is no history of bite, but contact with rat.	Bacteriological culture; Matrix-assisted laser desorption mass spectrometry (MALDI-MS).	Benzylpenicillin.
Mathé P, et al.[85]	32y/F	Hyperthermia, fatigue, arthralgia, and rash.	There is no history of bite, but contact with rat.	Bacteriological culture; Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-ToF MS).	Penicillin G.

There is a scarcity of studies investigating the agent in suspected animals. In none of the mentioned studies were samples collected from the animals or food involved. It represents a significant gap in the understanding of the infection's epidemiology. The lack of systematic sample collection from animals and food limits the comprehension of the transmission chain and hinders the implementation of effective preventive measures. Considering that rodents are the primary reservoirs of the pathogen, the absence of monitoring in pet, laboratory, and synanthropic animal populations reduces the ability to identify sources of infection. Additionally, the lack of investigation into contaminated food prevents the assessment of the role of ingestion in disease dissemination. To address these challenges, future investigations must include comprehensive sampling of animals and food/water, along with the development of active surveillance strategies involving interdisciplinary approaches. Robust epidemiological studies, employing advanced identification techniques, can provide more precise data on pathogen circulation and enable more effective control measures to mitigate the impact of the infection on public health. The training of healthcare professionals for the early recognition of the disease is essential. This includes regular training for physicians, veterinarians, and other public health professionals, with an emphasis on identifying early symptoms, distinguishing them from other nonspecific febrile infections, and adopting rapid diagnostic protocols. Additionally, the development of updated clinical guidelines is crucial to support decision-making regarding necessary laboratory tests and the initiation of appropriate antimicrobial therapy, emphasizing the importance of antibiograms in assessing the agent's susceptibility. Strengthening the integration between human and veterinary health services is also necessary to ensure an efficient flow of information on suspected cases and preventive measures. It is important to emphasize that the success of clinical resolution is directly linked to early identification and the immediate initiation of specific treatment.

Diagnosis

The diagnosis of *S. moniliformis* infection remains a challenge due to the difficulty of isolating the microorganism and its nonspecific clinical presentation, which can lead to confusion with other febrile illnesses. Isolation through bacterial culture is challenging due to its specific growth requirements and slow growth rate, which may delay the initiation of appropriate treatment.[1] Molecular methods, such as PCR, serological tests, and advanced techniques like mass spectrometry and chromatography, offer greater sensitivity and specificity, enabling faster and more accurate identification.[67,86] However, the limited availability of these methodologies, along with their high cost and the need for well-equipped laboratories, still represent significant obstacles. Another diagnostic challenge, as previously mentioned, is the difficulty healthcare professional's face in clinically identifying the disease, as its symptoms can be mistaken for those of other febrile illnesses. Awareness of the disease, particularly among physicians and veterinarians, is essential for early and accurate diagnosis. A detailed anamnesis, including a history of contact with rodents or potentially infected animals - even in the absence of a bite - as well as the possible ingestion of contaminated food or water, should be recognized as a key diagnostic tool. Additionally, the implementation of standardized protocols for screening suspected cases can help reduce under diagnosis, prevent the disease from being overlooked, and optimize clinical management. The following section will discuss the methodologies used for microorganism identification and definitive diagnosis.

Culture and isolation

As previously mentioned, *S. moniliformis* is a fastidious microorganism that requires enriched culture media containing 5-20% blood, serum, or ascitic fluid for growth,[12,86] and does not cause hemolysis on blood agar.[20] According to the literature, the initial isolation of the agent requires anaerobic conditions, though subsequent cultures can be carried out under microaerophilic conditions. This differs from the isolation of samples derived from *Cavia porcellus*, which require anaerobic conditions for culture and isolation regardless of the phase.[12] The culture is performed at 35-37ºC in an atmosphere containing 5-10% CO_2,[2,86] and growth may take 2-10 days in liquid media. In solid media, colony observation may be possible from the 3rd day of incubation.[2,11,13] It should be noted that culturing and isolating the agent from healthy carrier animals is quite challenging,[18] but it remains the most commonly used methodology for initial isolation and subsequent identification.[44] Typical colonies in liquid media appear cotton-like,[1] while colonies grown on agar are circular, convex,

grayish or colorless, smooth, shiny, and with fringed edges. Some colonies may exhibit a "fried egg" appearance, observed in the L form after several days of culture.[1,11,14] There are reports of the agent being inhibited by the polyanionic detergent sodium polyanethole sulfonate (SPS), an anticoagulant used in commercially available blood culture bottles.[3] This factor must be considered to avoid false negative results. The development of the L-form, which is cell-wall deficient and penicillin-resistant, occurs spontaneously or when challenged with penicillin.[11] L-form colonies have a "fried egg" appearance with a dark center, closely resembling Mycoplasma sp. colonies. Visualization of the L-form can be facilitated using Dienes staining in smears.[11,12] After culture and isolation, biochemical tests are required for confirmation. Regarding biochemical characteristics, Table 1 outlines the expected results for the two forms of *S. moniliformis*. There are no significant differences between them. The microorganism can ferment a variety of carbohydrates and alcohols with acid production without gas. Acid production from the fermentation of sugars such as fructose, maltose, mannose, lactose, sucrose, trehalose, and xylose may vary depending on the medium used for culture.[11,12]

Table 1 Expected results for biochemical tests commonly used for the identification of *S. moniliformis*

Test	Results		Test	Results	
	Common form	**L-phase variant**		**Common form**	**L-phase variant**
Oxidase	Negative	Negative	Urea Hydrolysis	Negative	Negative
Catalase	Negative	Negative	Esculin hydrolysis	Weak reaction	Weak reaction
Indole	Negative	Negative	Glucose fermentation	Positive	Positive
Nitrate	Negative	Negative	Galactose fermentation	Weak reaction	Positive
Hydrogen sulfide	Negative	Negative	Maltose fermentation	Weak reaction	Positive
Aginine hydrolysis	Positive	Positive	Mannose fermentation	Weak reaction	Weak reaction
Methyl red	Negative	Negative	Other carbohydrates	Negative	Negative
Phenylalanine deaminase	Negative	Negative	TSI agar with serum (butt/slant)	Acid/acid	Acid/acid
Citrate	Negative	Negative			

Source: Elliott SP, Hayashimoto N, Yoshida H, et al.[1,2]

Serology

- Immunoblot

According to Boot, Van de Berg, and Vlemminx, the use of Western Blot or Immunoblot can be a valuable tool for the detection of antibodies, offering greater specificity than the ELISA technique.[87]

- Enzyme-linked immunosorbent assay (ELISA)

The enzyme-linked immunosorbent assay (ELISA) is a diagnostic tool that can be utilized for the detection of the agent (direct ELISA) and/or for the detection of IgM and/or IgG antibodies (indirect ELISA).[88] Regarding the indirect ELISA, it is important to note that antibodies may be found in infected rats 2 to 4 weeks after infection,[23] and in mice, the animals commonly succumb before antibodies can be detected, with variations observed among different strains.[26,28,88] Boot, Van den Berg, and Lith mentioned in their study the potential use of indirect ELISA for screening, followed by PCR for confirmation of the etiological agent.[21] It should be noted that, depending on the type of antibody present, the host may have had contact with the agent and may no longer be a carrier. Koopman et al. and Boot et al. proposed protocols for monitoring rodent colonies for the detection of antibodies using indirect ELISA.[23,89] ELISA showed higher efficiency in detecting positive results compared to bacterial culture; however, it is important to emphasize that, as previously mentioned, this test has lower specificity, and therefore immunoblot is more suitable for confirming positive or doubtful reactions in ELISA.[88] Eisenberg et al.,[42] also mentioned in their study that the use of membrane proteins compared to whole bacterial cells may increase the specificity of the ELISA test.[88] Boot, Van den Berg, and van Lith[24] conducted a study in which they inoculated the agent via oral and intranasal routes in six strains, evaluating the immune response of the animals through ELISA on days 9, 12, 21, and 33 post-infection. For the detection of antibodies, the authors utilized sheep anti-rat IgG as a secondary antibody, following the methodology proposed by Boot et al.[89] They observed that all strains showed a significant response regarding antibody production on day 21 post-infection, with no alterations among them. On day 33, the Wistar Kyoto and SHR strains exhibited the highest concentrations, in contrast to the BN and F344 strains, which showed the lowest.[24]

Molecular biology

Reports in the literature demonstrate that different primers are utilized for the detection and identification of the agent by PCR.[12] The PCR protocols described for the detection and identification of *S. moniliformis* are frequently associated with partial sequences of the 16S rRNA gene,[45,88] despite previously noted difficulties in unequivocally identifying the pathogen using this method. Nolan et al.,[90] published a study in which they performed the complete genomic sequencing of strain 9901 of the agent.[90] Boot, Oosterhuis, and Thuis[18] used primers based on the nucleotide sequence of the 16S rRNA gene from 11 strains of *S. moniliformis*, producing a 296 bp amplicon. According to the authors, this analysis demonstrated good sensitivity; however, concerning specificity, failures were observed due to similarities with the genus *Leptotrichia.*[18] Kimura et al. published a study in which they resolved the specificity issues of the protocol used by Boot, Oosterhuis, and Thuis, amplifying a 269 bp fragment.[18,46] Eisenberg et al. proposed modifications to the protocol of Kimura *et al.* [46], altering the annealing temperature and time.[88] Rohde, Rapsch, and Fehr, employed another PCR protocol in which they utilized a primer pair SbmF/SbmR, producing a longer amplicon and thereby further improving the specificity of the analysis.[91] Both protocols yielded significant results for detecting strains of *S. moniliformis* from humans, rats, and mice. Fawzy et al. mentioned in their study that other genes, such as gyrB, groeL, and/or recA, could be utilized to assist in species differentiation, thereby increasing the specificity of the test.[86] Table S2 presents the primers and PCR programs utilized in protocols described in the literature.

Table S2 Primers and PCR programs used in protocols for the detection and identification of *S. moniliformis*.

Target gene	Primer	Sequence (5´-3´)	PCR program	Expect PCR product	Study
16S rRNA	S5	CATACTCGGAATAAGATGG	(95°C/ 180secs) x1; (95°C/ 20secs, 53°C/60secs, 72°C/60secs) x35; (72°C/420secs) x1. Eisenberg et al. (2014) proposed modifications, changing the annealing temperature (53°C) and time (60secs).	269bp	Kimura M, et al;[46] Fawzy A, et al.[86]
	AS2	GCTTAGCTCCTCTTTGTAC			
16S rRNA	SbmF	GAGAGAGCTTTGCATCCT	(94°C/240secs) x1; (94°C/ 60secs, 50°C/60secs, 72°C/60secs) x35; (72°C/420secs) x1.	1.222bp	Rohde J, et al.[91]
	SbmR	GTAACTTCAGGTGCAACT			
16S rRNA	S	GCTTAACACATGCAAATCTAT	(95°C/180secs) x1; (95°C/ 20secs, 67°C/60secs, 65°C/60secs, 63°C/60secs, 61°C/60secs, 59 °C/60secs) x1; (72°C, 60secs) x1; (57°C/60secs) x35.	296bp	Boot R, et al.[18]
	AS	AGTAAGGGCCGTATCTCA			
	F27	AGAGTTTGATCMTGGCTCAG			
16S rRNA	1392R	ACGGGCGGTGTGTRC	There is no information.	1.288bp	Kawakami Y, et al.[72]
	F27	AGAGTTTGATCMTGGCTCAG			
16S rRNA	1541R	AAGGAGGTGATCCAGCCGCA	There is no information.	1.468bp	Addidle M, et al.[65]
gyrB	MZK-F	AAGATAGGGTAATGCTTACAGAAGGAG	There is no information.	514bp	Hayashimoto N, et al.[2]
	MZK-R	AATCTACCTTGTTTTGCAGATCCAC			
rpiL	Smon_PF2515_F1_3	AGAGAAACTCAATGCAGAATTAGAGGACTATAA	(95°C/180secs) x1; (95°C/10secs) x40; (63°C/30secs) x1.	171bp	Kelly AJ, et al.[9]
	Smon_PF2515_R3	CCTCTTTCTAAGTTGTCCAAGTTTTCTA			
	Smon_PF2515_P3_2	TCTAAAAGAAAAGAAAAGGAATTACAGGAATAT			
gyrB	Smoni-gyrB-F	AGTTTAAAATTCCCTGAACCACAATT	(95°C/180secs)x1; (95°C/15secs)x40; (60°C/45secs)x1.	96bp	Passaretti T, et al.[17]
	Smoni-gyrB-R	ACTTCCAAACACTCCTGAAACTATACTTG			

Fatty acid profile

For diagnosis, fatty acid profiling can also be performed using liquid or gas chromatography techniques. The main fatty acid peaks observed are tetradecanoic acid (C14:0), palmitic acid (C16:0), linoleic acid (C18:2), oleic acid (C18:1), and stearic acid (C18:0).[1,12,13]

Other methodologies

Mass spectrometry has been used as a diagnostic tool for the identification of the agent. Mackey et al. mentioned the use of electrospray ionization followed by mass spectrometry (ESI-MS) from synovial fluid samples.[67] Suzuki et al. and Torres-Miranda, Moshgriz, and Siegel noted the use of matrix-assisted laser desorption ionization time-of-flight mass spectrometry for identification from blood[76] and synovial fluid samples,[47] respectively. Additionally, Szewc et al. also utilized the same technique for identifying the strains used in their study.[3]

Treatment and antimicrobial susceptibility

According to the scientific literature, treatment primarily involves the use of antimicrobials. The U.S. Centers for Disease Control and Prevention (CDC) recommends the use of penicillin, cephalosporins, carbapenems, aztreonam, clindamycin, erythromycin, nitrofurantoin, bacitracin, doxycycline, tetracycline, teicoplanin, and vancomycin as effective treatment options.[92] The therapeutic choice, with penicillin as the first-line drug,[6,59,85] is effective when initiated early. However, a lack of familiarity with the disease can lead to delayed diagnoses, increasing the risk of severe complications. Antimicrobial resistance must also be monitored, given sporadic reports of treatment failures, as observed in analyzed studies. The development of new therapeutic strategies is crucial for expanding treatment options for affected individuals. This includes the investigation of alternative antibiotics and combination therapies, which may be a promising approach to preventing bacterial resistance and improving clinical outcomes. The use of novel broad-spectrum antimicrobial agents, along with studies on resistance mechanisms and immune responses, should also be prioritized and systematically conducted in all cases involving the pathogen. The identification of circulating strains and their susceptibility to antimicrobial agents is essential to ensuring patient recovery.

Conclusion

S. moniliformis continues to be considered a rare bacterium; however, it holds significant zoonotic importance. Its association with rat-bite fever and Haverhill fever underscores the need for surveillance, particularly in areas with large populations of synanthropic rodents. Although its prevalence is low, according to the literature, its impact on human health can be severe, with symptoms ranging from fever and arthritis to potentially fatal complications such as septicemia. The nonspecific nature of the symptoms makes diagnosis challenging, increasing the risk of complications when diagnosis is delayed or incorrect. Rapid and accurate diagnosis of these diseases remains problematic due to the limitations of traditional methods, such as bacterial culture, which is hindered by the requirements for isolating the microorganism. However, advances in diagnostic tools, such as mass spectrometry and chromatography, are enabling faster diagnoses, though at a higher cost. The zoonotic nature of the disease necessitates heightened attention from healthcare professionals involved with affected individuals, whether human or animal. *S. moniliformis* infection can be considered rare, as documented cases are infrequent compared to other zoonoses. Its low incidence may be attributed to factors such as underreporting, diagnostic challenges, and lack of clinical suspicion. However, it can also be regarded as a neglected disease because, despite its zoonotic significance and potential for severe complications, it receives little attention from the scientific community and health authorities. The lack of awareness among healthcare professionals, the absence of standardized protocols, and difficulties in diagnosis contribute to this neglect. It is important to mention that diseases considered rare may actually be neglected, especially when there are no substantial efforts directed towards diagnosis, treatment, or epidemiological surveillance.

The treatment of the disease depends on the use of antimicrobials, and its success is directly linked to the speed of diagnosis, as delays can lead to serious complications. Therefore, early detection and the administration of appropriate medications are crucial to ensure positive outcomes for patients. Healthcare professionals' knowledge and the implementation of better investigative and epidemiological surveillance strategies are essential for identifying suspected cases, accurately elucidating cases, and reducing severity. In terms of control and prevention, regular monitoring of rodent populations in urban and rural environments, as well as pets and laboratories, is essential. Routine health control of rodents used in scientific research, veterinary monitoring of pets, and epidemiological studies in areas with high rodent incidence are necessary to achieve these goals. Only through an integrated approach - combining advanced diagnostics, effective treatments, and active surveillance – will it be possible to mitigate the impact of this pathogenic agent on public health.

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Conflicts of interest

The authors declared that there are no conflicts of interest.

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