GV-SOLAS
Gesellschaft für Versuchstierkunde
Society for Laboratory Animal Science

Expert Information

From the Working Group on Hygiene

Implication of infectious agents on results of animal experiments

Streptobacillus moniliformis

Status April 2024

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Contents

Streptobacillus moniliformis (*S. moniliformis*)

Background

- *Streptobacillus* (*S.*) *moniliformis* is the main causative agent of the bacterial zoonosis rat-bite-fever (RBF) in humans and its food-borne variant, Haverhill fever.[1-3]
- Another form of rat-bite-fever called Sudoku is caused by '*Spirillum minus'* (no valid species/ i.e. not listed in "Approved List of Bacterial Names")
- RBF was first reported in the United States in 1839[4], but was not associated with a specific pathogen until 1914, when Schottmüller described *Streptothrix muris ratti*, isolated from a rat-bitten man.[5]
- In 1925, the organism was renamed *Streptobacillus moniliformis*[1]
- A milk-associated outbreak of disease occurred in Haverhill (MA, USA) in 1926[6]. The organism found at this time was named *Haverhillia multiformis* by Parker and Hudson[7], although most likely it represents *S. moniliformis*.
- RBF occurs worldwide and is believed to be under-recognized and under-diagnosed in humans.[8,9]

Prevalence

- High prevalence of approximately 50–100% in wild rats.[3,10-12] Also high prevalence in pet rats,[13,14] but rare in laboratory rats and mice,[15] and in wild mice.
- *S. moniliformis* was common in laboratory rats in the first half of the last century.[16]
- Wild rats usually carry *S. moniliformis* asymptomatically in their oro- or nasopharynx.[3,10]
- Most documented outbreaks (epizootics) of streptobacillosis in mice were due to rats maintained in the same room or in vicinity and *S. moniliformis* transmission via aerosols or handling by animal caretakers,[17,18] though in some epizootics rats could not be identified as a source of infection.[19-22]

Host species

- Rats (Norway rats, *Rattus norvegicus*) are the natural host[12] which most often harbour the microorganism without clinical signs.
- Mice (*Mus musculus*) are not a natural reservoir for *S. moniliformis*.[8]
- *S. moniliformis* has been found in laboratory rats,[23-25] pet rats,[14,26, 27] feeder rats[28] and has also been isolated from laboratory mice.[19,21,22, 29]
- Other rodents, companion and exotic animal species as well as livestock were reported to be susceptible to infection and clinical disease.[8,22,30-36]
- Isolates from rats, mice, turkeys and humans were shown to belong to the same species.[37]

Properties

- Commensal inhabitant of the nasopharynx of rats and shed in oral, nasal or ocular secretions of infected animals,[3] and in urine and faeces.[3,38,39] *S. moniliformis* is usually transmitted to humans through saliva by bite or scratch,[8,27,38,40-45] but also by handling animals, by exposure to their excreta or saliva,[3,46-48] or by consumption of contaminated

food or drinking water.[49,50] Transmission through fomites and aerosols is discussed.[51,52].

- Persistence: in mice, the persistence of *S. moniliformis* ranges from none[38] to six months in joints after intravenous infection of Swiss Webster mice.[53] One report indicated the persistence of the organism in a mouse for 16 months.[54]
- Resistance to environmental conditions: The organism does not form spores and is thought to have no significant environmental persistence. Normal environmental decontamination procedures should be sufficient to remove S. moniliformis from the environment.[55]

Susceptibility

- As *S. moniliformis* is a natural commensal of the wild rat nasopharynx, it can also colonize laboratory rats without clinical signs of disease.[3,56] Differences in susceptibilities of different strains are not described.
- In mice, strain-dependent susceptibility is described: C57BL/6 and outbred Swiss mice are very susceptible to clinical infection, DBA/2 mice intermediate in susceptibility, and BALB/c, CB6F1, B6D2F1 and C3H/He mice do not show clinical signs of infection.[19,21,22,29,57]
- Successful experimental infection through subcutaneous, intraperitoneal, intravenous, nasal, oral and conjunctival routes is described.[17,22,53,57-59]

Organotropism

- In rats, *S. moniliformis* is described to be part of the commensal microbiota of the nasopharynx.[3,16,60]
- In healthy rats, *S. moniliformis* was also isolated by culture from the larynx, upper trachea, lung, submandibular and cervical lymph nodes, and middle ear.[24,56,60-63]
- In mice following natural infection*, S. moniliformis* was isolated from submaxillary and cervical lymph nodes, blood, spleen, kidney, seldom from vagina, nasopharynx, liver and lung, and never from caecal contents and urine.[22]

Clinical disease

Rats

- Generally, rats are asymptomatically colonized.[3,56] Only rarely, opportunistic pulmonary infections or abscesses were described.[13,22]
- Bronchopneumonia, otitis media and conjunctivitis were described caused by *S. moniliformis* in conjunction with presumptive pathogens such as *Rodentibacter spp.*, *Mycoplasma pulmonis* and others.[16,25,60,62,64,65]
- Adult rats are usually resistant to experimental parenteral inoculation, but neonates may develop pneumonia.[16,60,62] Experimental intravenous infection of young rats caused polyarthritis with swelling, redness, tenderness and stiffness of joints, which subsided 10 to 30 days after the acute phase in most animals.[66,67]
- The prior death of a rat was sometimes mentioned in cases of human RBF.[38]

Mice

- Mouse strains differ in their susceptibility to infection and may strain-dependently develop disease. Severe clinical symptoms were only observed in C57BL/6J, Swiss White and Swiss Webster mice and in some DBA/2J mice.[19,22,38,53,57]
- Typical clinical signs range from ruffled coat, bended back, ocular discharge due to conjunctivitis, emaciation, heavy weight loss, diarrhoea, enlargement of cervical lymph nodes (cervical lymphadenitis), dyspnoea, anaemia, haemoglobinuria, to swelling of the limbs and tail, and polyarthritis with lameness.[17,19,53,57,68]
- In highly susceptible strains, infection results in septic lymphadenitis, polyarthritis and multi-organ microabscesses leading to septicaemia, cachexia, and sudden death.[19,38,53,69] If animals survive the acute stages of disease, a more prolonged septicaemia course with polyarthritis, most commonly of the joints of the hind extremities and the tail, swellings, osteomyelitis and abscesses is seen.[22]
- Septicaemia and death was induced after subcutaneous infection within 1 to 8 days in 58%, after intraperitoneal infection in 83%, after oral infection in 31% and after intranasal infection in 48% of mice.[17]
- Young mice were more susceptible to infection than old mice.[20]

Guinea pigs

- Isolates from guinea pigs, which were formerly assigned as *S. moniliformis,* form a separate genus and have recently been described as *Caviibacter abscessus.*[70]
- Independent of the route of infection, *C. abscessus* does not cause generalized or systemic disease in guinea pigs,[71] but regionally limited symptoms with unilateral, rarely bilateral purulent lymphadenitis of the submaxillary and cervical lymph nodes.[71-74]
- There is one report of a guinea pig with granulomatous nodular pneumonia without lymphadenitis.[75]
- Spontaneous recovery without any treatment within 3 - 8 weeks is described.[71]

Pathology

- In rats, experimental oral and intranasal infections of several inbred strains did not yield any gross lesions in the respiratory tract.[23,56, 61]
- In mice, *S. moniliformis*-associated gross alterations are only found in highly susceptible mouse strains (e.g. C57BL/6, Swiss white mice) with a clinically apparent infection.[19,21,22,53,57,68]:
  - Splenomegalia and hepatomegalia with multiple purulent necrotizing foci
  - Purulent to necrotizing pneumonia and lung abscesses
  - Ascites
  - Multiple enlarged lymph nodes (purulent to necrotizing lymphadenitis, in particular *Lnn. tracheobronchiales*, *Lnn. mandibulares* and *cervicales*, *Lnn. axillares* and *inguinales*), and ulcer of the skin
  - Progressive fibrinopurulent arthritis and osteomyelitis with peri-articular abscesses and necrosis, periostitis and fibrous connective tissue proliferation
  - embolic interstitial nephritis in the course of subacute sepsis
- Pathologic findings in cases of acute septicaemia are few.[19]

Morbidity and mortality

- Usually no morbidity or mortality in rats[56]
- Strain-dependent high morbidity and mortality in mice[19,22,38,57]
- All infected C57BL/6 showed clinical signs within 2-3 days.[56] Mortality between 35% and 75% in C57BL/6, and of up to 100% in a colony of Swiss white mice in the course of an epizootic[19,22,57]
- No clinical signs in BALB/c[57]

Zoonotic potential

- Although streptobacillary RBF is rather rarely diagnosed, it is most likely under-reported worldwide due to a lack of awareness of the disease among clinicians, absence of pathognomonic signs of disease in humans and animals, lack of reliable diagnostics, fastidious growth of the pathogen, susceptibility to most antibiotics used for empiric therapy and unnoticed animal contact.[3,9,76] In addition, RBF is not a notifiable disease worldwide.
- People with direct or indirect contact to rats are particularly at risk of infection: homeless people, farmers, hunters and trappers, veterinarians and their employees, pest controllers, sewer workers, pet shop personnel and pet owners. Due to the increased popularity of pet rats, especially children are also a risk group.[3,8,9,77,78]
- The incubation period for RBF ranges from 3 to 21 days. RBF or food-borne HF is typically characterized by a triad of fever, arthritis and a maculopapular petechial or pustular rash. Acute disease symptoms also include malaise, headache, muscle pain, vomiting and pharyngitis.[3,8,9] Severe courses of infection may include life-threatening complications, including endo- and myocarditis, hepatitis, pericarditis, pneumonia, abscess formation, chronic arthritis, septicaemia, and meningitis.[8,28,38,43,45,79-84] Infants and children may experience anaemia and severe diarrhoea resulting in weight loss.[41, 78]
- Untreated RBF can lead to serious health complications and death. A mortality rate of up to 13% in untreated cases was reported that might be even much higher in cases with chronic tissue manifestations.[8,78]
- Prompt notification of wild or pet rat bites to a physician and immediate antibiotic treatment normally results in rapid improvement and resolution of infection.[3]
- Since wild mice are not considered a natural host of *S. moniliformis,* only a few human RBF cases were reported after a mouse bite.[85,86]
- Since *Streptobacillus sp.* infections are rare in laboratory rodents, zoonotic infections of animal caretakers, scientific staff or veterinarians are not very likely.

Interference with research

Oncology

- No data

Teratology

- Arrested pregnancy with foetal resorptions and abortions were observed in natural infection of pregnant mice.[59,87]

Infectiology / Interactions with other infectious agents

- No data

Immunology

- The Th1 immune response in C57BL/6 mice is not protective; pathologies are presumably caused in part by the relatively strong Th1 immune response.[57]
- Oral infection of C57BL/6J mice led to IgG production in 65% of animals, whereas only 5% of the DBA/2J and B6D2F1 mice produced IgG. This different reaction against *S. moniliformis* infection might be related to differential recognition by Toll-like receptors.[22] The more severe inflammatory reactions after infection could be explained by recognition of *S. moniliformis* by Toll-like receptors in C57BL/6J mice.[39]
- The presence of homologous antibodies prior to infection prolonged the incubation period for the development of the lesion.[20]
- *S. moniliformis* was resistant to destruction by *in vitro* phagocytosis and actually increased in number in the presence of phagocytes.[20]

Toxicology

- No data

Physiology

- No data

Cell biology

- No data.

Assisted reproductive technology

- No data

Special considerations

- Strict exclusion of wild, feeder and pet rats from laboratory rodent facilities
- Quarantine and testing of all incoming animals from non-commercial sources
- Serological tests are assumed to be superior to culture methods.[61]
- In infected rats, antibodies are found 2 to 4 weeks after infection,[24] also co-housed rats seroconvert.[61] In mice, strain-dependent disease may result in death before antibodies can be detected.[10]
- Evaluation of different sentinel systems revealed that cultural and serological investigations of these animals might not be sufficient to detect infection.[57]
- PCR detection is most successful in tissue samples from pharynx and mandibular lymph nodes, salivary glands, trachea and spleen 3 to 7 days after infection.[56]
- Reliable elimination of *S. moniliformis* by hysterectomy or embryo transfer[55]
- Staff working with laboratory rodents should not keep pet or feeder rats or work with wild rats
- Penicillin G is the most efficient antimicrobial substance (drug of choice in the treatment of RBF and HF) followed by tetracycline.[3,45]

- Treatments using antibiotics active on the bacterial cell wall (e.g. Penicillin) might induce the formation of cell wall deficient L-forms of *S. moniliformis* that may persist in the human body and cause relapses after stopping antibiotic therapy.[88,89]
- Incomplete pathogen elimination of *S. moniliformis* infection in C56BL/6 mice after antimicrobial treatment with ampicillin and tetracycline.[22]
- A long time the genus *Streptobacillus* was believed to be monotypic comprising *S. moniliformis* as the only species of this genus. Since 2015, five additional species have been named:
  - *Pseudostreptobacillus hongkongensis*, has been exclusively isolated from humans, and is considered to be part of the microbiota in the oropharynx.[90-92]
  - *S. felis*, isolated from a domestic cat (*Felis silvestris catus*) and a rusty-spotted cat (*Prionailurus rubiginosus*)[93-95] and from a human patient with rat-bite-fever-like disease[96]
  - *S. notomytis*, originally isolated from a spinifex hopping mouse (*Notomys alexis*)[97]. It was also isolated from black rats (*Rattus rattus*).[10,52,98] Meanwhile there are several cases of RBF in humans, which were caused by *S. notomytis* transmitted from black rats.[99,100] Infections of black rats in a zoo caused neurological signs including disorientation, torticollis, stall walking, ataxia and death.[52]
  - *S. ratti*, isolated from a black rat in Japan[10,12,101]
  - *S. canis* isolated from a dog (*Canis familiaris*)[102]

Katja Schmidt, Heidelberg, April 2024

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