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# Case report: A fatal case of aortic and mitral valve endocarditis caused by *Streptobacillus moniliformis*

Mette Winther <sup>1,2\*</sup>, Hanne Sortsøe Jensen <sup>3</sup>, Irene Harder Tarpgaard <sup>2</sup>, and Hans Linde Nielsen <sup>2,4</sup>

<sup>1</sup>Department of Clinical Microbiology, Aarhus University Hospital, Palle Juul-Jensens Blvd. 99, 8200, Aarhus, Denmark; <sup>2</sup>Department of Clinical Microbiology, Aalborg University Hospital, Denmark; <sup>3</sup>Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; and ; and <sup>4</sup>Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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## Background

Infective endocarditis (IE) secondary to rat-bite fever (RBF) is rare but potentially lethal. Rapid diagnosis is of utmost prognostic importance. However, the diagnosis of RBF is challenging because *Streptobacillus moniliformis* does not grow under conventional culture conditions.

## Case summary

A 65-year-old male without previous cardiac history presented with sudden onset of balance problems and facial palsy. For 2 weeks, he had experienced intermittent fever and myalgia. Transoesophageal echocardiography (TOE) revealed severe mitral and aortic valve IE with aortic root abscess. The patient underwent a double biological valve replacement. Blood cultures remained negative after 9 days of incubation. However, sub-cultivation on solid media demonstrated the growth of pleomorphic Gram-negative rods, identified as *S. moniliformis*. After 4 weeks of antibiotic therapy, he was discharged. One month later, control TOE showed valve excrescences and aortic annular aneurysm. Despite comprehensive surgery, antibiotic treatment, and intensive care, the patient died 1 week after reoperation.

## Discussion

A fatal outcome of *S. moniliformis* IE is rare. The majority of previous cases describe underlying valvular abnormalities or death due to insufficient antimicrobial therapy. Here, the patient had no prehistory of valvular heart disease and despite appropriate antibiotics, the outcome was fatal. Rapid diagnosis of RBF IE has prognostic implications. Identification of *S. moniliformis* is, however, difficult, because the bacterium is fastidious and does not grow under standard laboratory conditions. Therefore, diagnosis often relies on clinical symptoms or a history of rodent exposure. Close attention to this disease by clinicians, in addition to, dialogue with clinical microbiologists is essential.

## Keywords

*Streptobacillus moniliformis* • Infective endocarditis • Fatal outcome • Rat-bite fever • Zoonotic infection • Case report

## Learning points

- Possible rodent exposure several months before the diagnosis of infective endocarditis (IE) should be thoroughly explored.
- To prevent complications and a delayed diagnosis, collaboration between clinicians and clinical microbiologists is essential to improve *Streptobacillus moniliformis* identification as the bacteria cannot be grown under standard laboratory conditions.
- Close follow-up and extension of antibiotic therapy may be considered in patients with severe rat-bite fever IE.

\*Corresponding author. Tel: +45 27 26 68 77, Email: [mettejoh@rm.dk](mailto:mettejoh@rm.dk), [mjmail12@gmail.com](mailto:mjmail12@gmail.com)

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## Introduction

*Streptobacillus moniliformis* is the causative pathogen of rat-bite fever (RBF) in Europe and North America.<sup>1</sup> The bacterium is a fastidious Gram-negative bacillus found as a normal part of the oro- and nasopharyngeal microbiota of rats and transmission to humans occurs through contact with infected rodents.<sup>1,2</sup>

Rat-bite fever is a rare zoonosis that manifests as an acute systemic disease. Symptoms are characterized by fever, headache, maculopapular rash, and migratory polyarthritis.<sup>1</sup> Reported complications include meningitis, focal abscesses, and infective endocarditis (IE).<sup>3</sup> The estimated overall mortality rate of untreated RBF is 7–13%.<sup>1,4,5</sup>

As RBF IE is potentially lethal, the diagnosis of streptobacillosis has important prognostic implications. However, identification of *S. moniliformis* is challenging as the bacterium does not grow under standard laboratory conditions. Therefore, diagnosis depends on clinical symptoms in combination with a history of relevant exposure. Here, we report a fatal case of native aortic and mitral valve IE secondary to *S. moniliformis* bacteraemia.

## Timeline

Approximately 2 months prior to admission	Rate bite in several toes
Day 1	Admission to hospital.
Day 6	Transoesophageal echocardiography (TOE) revealed severe infective endocarditis (IE). Initiation of intravenous meropenem 2 g two times daily for blood culture-negative IE.
Day 7	Surgical management of IE.
Day 13	Increased meropenem dosage to 2 g three times daily and the addition of gentamicin 3 mg/kg (according to Danish guidelines on blood culture-negative IE).
Day 17	Identification of <i>Streptobacillus moniliformis</i> (by sub-cultivation).
Day 19	Antibiotic treatment was switched to benzylpenicillin 3 g four times daily plus gentamicin 3 mg/kg.
Day 34	Completion of the antibiotic course. The patient was discharged without clinical or TOE signs of infection to a rehabilitation facility.
Day 66	Control TOE revealed valve excrescences, aortic annular aneurysm, and loosening of the mitral valve prosthesis. Administration of benzylpenicillin 3 g four times daily plus gentamicin 3 mg/kg was initiated.
Day 74	Reoperation.
Day 81	Patient died.

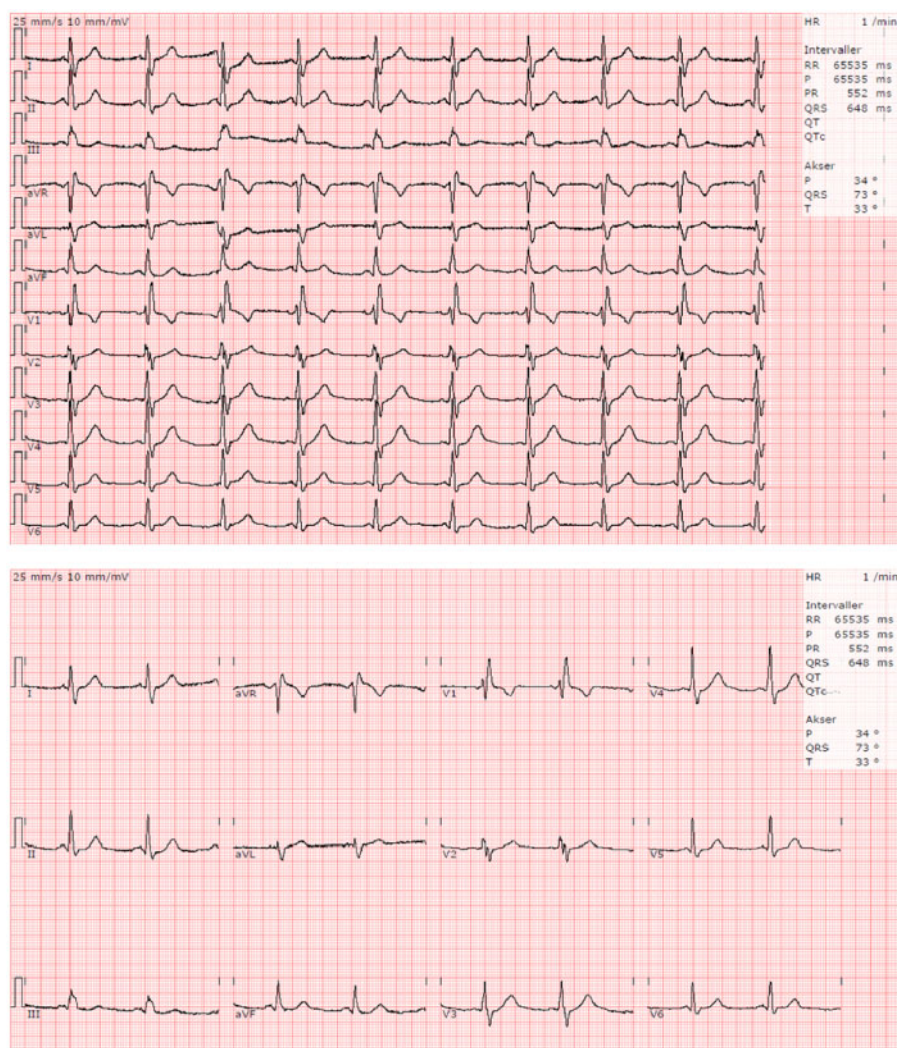
## Case presentation

A 65-year-old Danish male with a medical history of type 2 diabetes and hypertension was admitted to the hospital with suspicion of ischaemic stroke due to sudden onset of balance problems and facial palsy. For 2 weeks, the patient had experienced discomfort, intermittent fever, and myalgia. On examination, he was afebrile and vital parameters were normal. The patient presented no cardiovascular symptoms, and the cardiovascular examination was normal. Electrocardiogram showed sinus rhythm and right bundle branch block (Figure 1).

Blood tests showed a C-reactive protein level of 135 mg/L, haemoglobin 7.3 mmol/L, and creatinine 141 µmol/L, but normal leucocyte and platelet count of  $6.4 \times 10^9/L$  and  $167 \times 10^9/L$ , respectively. Other laboratory results were also within the normal range. Magnetic resonance imaging of the brain demonstrated ischaemic changes involving both the cerebellar hemispheres and the right frontal lobe (Figure 2). Computed tomography (CT) of the chest, abdomen, and pelvis showed a minor splenic abscess and intravenous cefuroxime 3 g every 8 h was initiated on suspicion of acute cardioembolic cerebral infarction given the manifestations in the brain and spleen. Six days after admission, a transoesophageal echocardiography (TOE) verified severe mitral valve and aortic valve IE with aortic root abscess (Figure 3A, Videos 1 and 2), and the antibiotic therapy was changed to intravenous meropenem 2 g every 12 h for presumed blood culture-negative IE (BCNIE). The following day, the patient underwent double biological valve replacement, debridement, and irrigation of the aortic root abscess.

In total, one blood culture set was obtained prior to the initiation of antibiotic treatment and two sets after antibiotic administration. After 9 days of incubation, blood cultures (BD BACTEC™ FX) remained negative, but a sub-cultivation of one primary aerobic bottle onto solid media (10% horse blood agar plates, incubated at 35°C in 5% CO<sub>2</sub>) was performed and yielded growth of Gram-negative pleomorphic rods 4 days hereafter. By the use of MALDI TOF-MS (Biotyper 3.1, Bruker Daltonik, Germany), the bacterium was identified to species-level as *S. moniliformis* (log-score 2.410) and whole-genome-sequencing was performed using the Illumina MiSeq instrument, confirming the isolate as *S. moniliformis* (data not shown). In addition, *S. moniliformis* was detected on both heart valves by 16S rRNA sequencing. Antimicrobial susceptibility testing was performed by using Etest (BioMérieux, Marcy l'Etoile, France) according to the EUCAST pharmacokinetics/pharmacodynamics (non-species related) breakpoints. The isolate was susceptible to benzylpenicillin (MIC: 0.016 mg/L) and ceftriaxone (MIC: 0.016 mg/L).

On further questioning after *S. moniliformis* identification, the patient recalled having been bitten by rats in several toes ~2 months prior to admission. Intravenous meropenem was later increased to 2 g every 8 h in combination with intravenous gentamicin 3 mg/kg every 24 h. Administration of gentamicin was terminated after 10 days due to high serum-gentamicin levels (data not shown). Hereafter treatment was switched to definitive therapy with intravenous benzylpenicillin 3 g every 6 h.



**Figure 1** Initial electrocardiogram showed sinus rhythm and right bundle branch block.

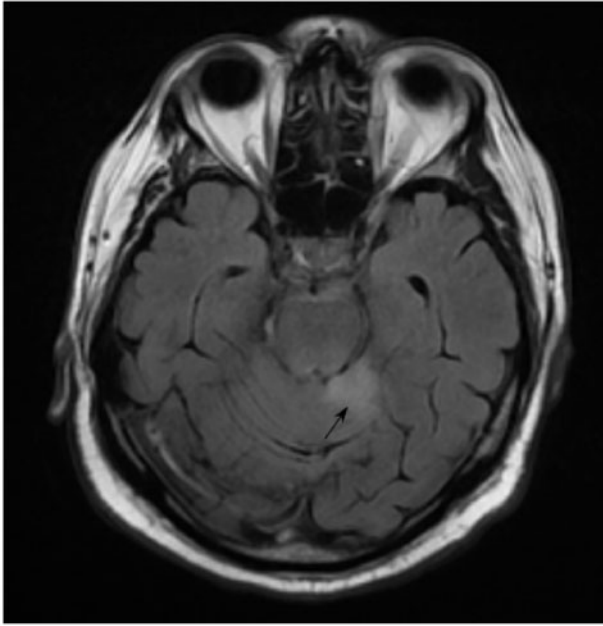
The post-operative course was complicated by third-degree atrioventricular-block with the need for permanent pacemaker implantation. After 4 weeks of antibiotic treatment, control TOE showed no pendulous excrescences (Figure 3B), and the patient was discharged. However, at 1-month follow-up visit a TOE revealed severe valve excrescences, aortic annular aneurysm, and loosening of the mitral valve prosthesis (Figure 3C,D). Cardiac CT showed severe tissue destruction in the aorto-mitral area (Figure 4). Blood cultures, in addition to, sub-cultivation on solid media were performed, but the growth of *S. moniliformis* was not detected. One week later, reoperation was performed including double valve replacement. Post-operatively, the patient developed biventricular heart failure requiring veno-arterial extracorporeal membrane oxygenation. Despite comprehensive intensive care, the patient died 1 week post-operatively.

## Discussion

This is the first fatal case of IE caused by *S. moniliformis* in Denmark, and to our current knowledge, the first fatal case treated with antimicrobial agents in Europe. The prevalence of RBF is rare. The disease may, however, be underdiagnosed due to a lack of information on rodent contact and presentation of non-species-specific clinical symptoms.

The prevalence of IE secondary to RBF is rare but uncertain. Nevertheless, this complication is the best described with a reported mortality rate as high as 53%.<sup>1,5,6</sup> A majority of previous reports have described underlying cardiac valvular abnormalities, mostly rheumatic, or death as outcome in absence of effective antibiotic therapy or inadequate antibiotic dosing.<sup>1,6-8</sup> In literature, only 26 cases with native valve RBF IE have been reported.<sup>5</sup>

Isolation and identification of *S. moniliformis* from clinical samples have recently been thoroughly reviewed by Eisenberg *et al.*<sup>9</sup> Sodium polyanethol sulfonate, an anticoagulant, present in most commercial



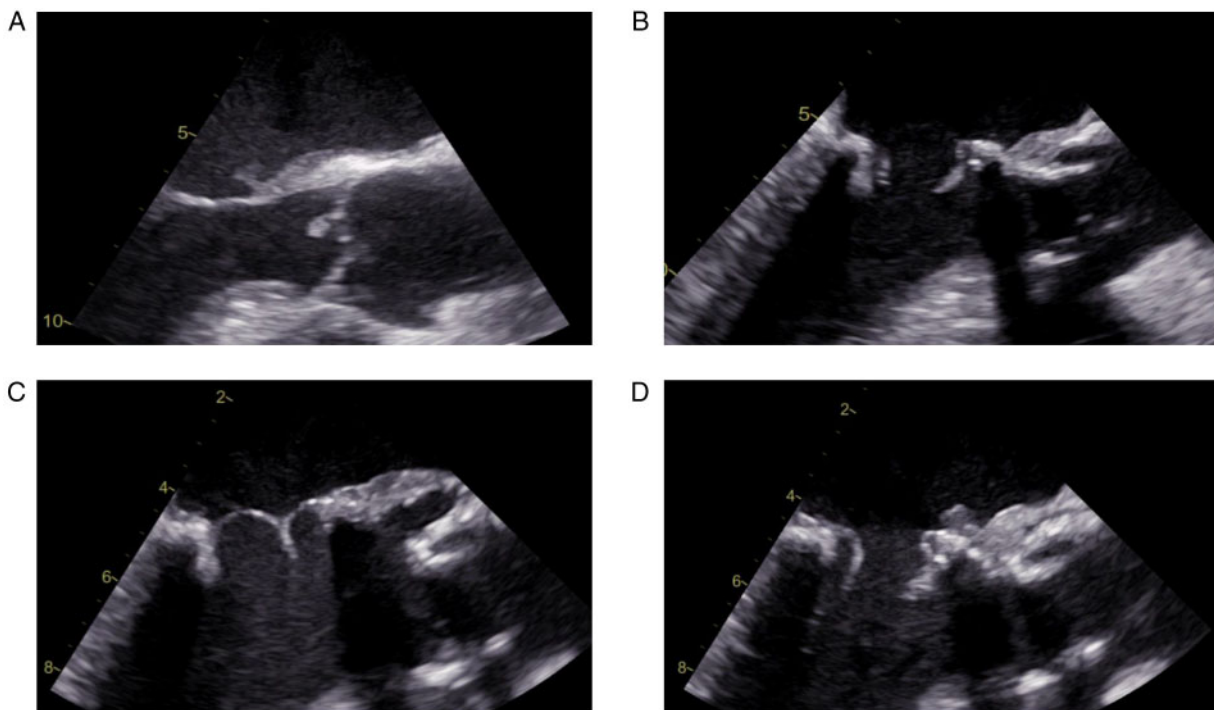
**Figure 2** Magnetic resonance imaging of the brain (T2 FLAIR) demonstrated ischaemic changes in the cerebellar hemispheres.

blood culture bottles inhibits the growth of *S. moniliformis* and therefore challenges isolation from routine blood cultures.<sup>9,10</sup> In addition, *S. moniliformis* is a fastidious bacterium requiring microaerophilic growth conditions and benefits from added CO<sub>2</sub> (5–10%). For optimal cultivation, enriched artificial media is preferable.

In the present case, all aerobic and anaerobic blood cultures remained negative in the BACTEC™ FX blood culture system after 14 days of incubation. Due to clinical suspicion of IE, sub-cultivation was performed in order to detect potentially fastidious microorganisms. This method is described in the 2015 ESC Guidelines for the management of IE.<sup>11</sup> In addition, the guideline proposes a diagnostic strategy for BCNIE including serological testing as well as rheumatoid factors and polymerase chain reaction. Several studies have shown that serological evaluation may aid in diagnosis in BCNIE.<sup>12,13</sup> However, no serological tests for RBF are available. A reliable method for species identification of *S. moniliformis* is the use of MALDI TOF-MS.<sup>9</sup> 16S rRNA gene sequencing can be used, but insufficient species resolution of 16S rRNA gene sequencing is possible.<sup>5,9</sup>

Due to the rarity of RBF IE, no treatment guidelines exist. However, high-dose benzylpenicillin (12 g/day) for 4 weeks in combination with gentamicin for the initial 2 weeks has been recommended.<sup>1</sup> Our isolate was fully susceptible to penicillin, and therefore interpreted as fully susceptible to carbapenem. According to literature, no *in vitro* resistance to penicillin has been described.

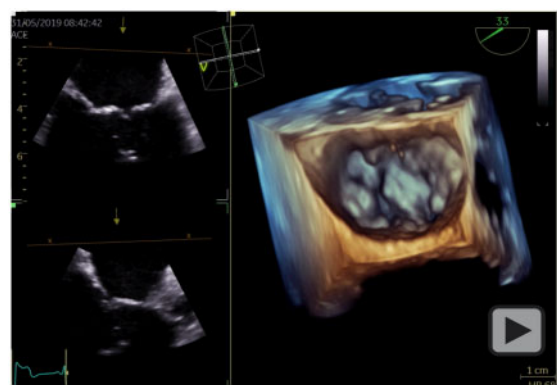
In the present case, the patient was not known with a prehistory of valvular heart disease and despite apparent *in vitro* susceptibility, treatment failed. The cause of this failure is uncertain. Nevertheless,



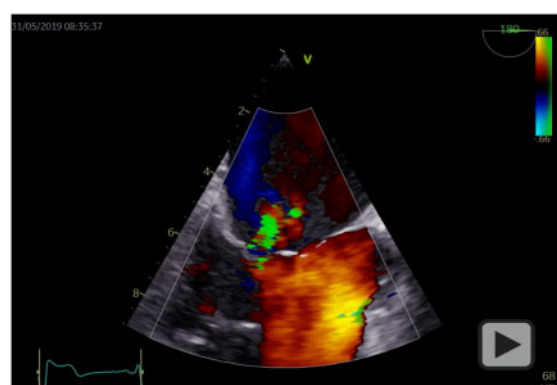
**Figure 3** (A) Diagnostic transoesophageal echocardiography revealed severe aortic valve and mitral valve infective endocarditis as well as aortic root abscess. (B) Transoesophageal echocardiography before discharge showed no pendulous excrescences. (C, D) Control transoesophageal echocardiography 4 weeks after discharge showed severe valve excrescences, aortic annular aneurysm, and loosening of the mitral valve prosthesis.



**Figure 4** Cardiac computed tomography showed severe tissue destruction in the aorto-mitral area. Left anterior descending artery (LAD).



**Video 1** (Diagnostic TOE): Echo-loops and 3D-loop of the mitral valve.



**Video 2** (Diagnostic TOE): Colour Doppler loop of the mitral and aortic valve.

even though identification of *S. moniliformis* was successful, the diagnosis was delayed due to lack of an exposure history, non-specific symptoms, and difficulties in culture diagnosis, i.e., lack of growth in blood cultures under standard conditions. Due to the fatal outcome presented here, we advocate for a treatment duration of 6 weeks, in addition to, a closer follow-up regimen.

## Conclusion

Given the risk of complications and potential lethal outcomes of RBF, the diagnosis of streptobacillosis has important prognostic implications. Identification of *S. moniliformis* is, however, difficult as the bacterium does not grow under standard laboratory conditions. Therefore, close attention to this disease by clinicians including exposure history in patients with severe IE along with a dialogue with clinical microbiologists is of utmost importance.

## Lead author biography



Mette Winther is a graduate from Medical School at Aarhus University, Denmark, in 2009. In 2016, she earned her PhD from Aarhus University and is currently a specialty trainee at Department of Clinical Microbiology at Aarhus University Hospital, Denmark. Microbiological areas of particular interest to Mette Winther include bacteria associated with IE. In addition, she is a board member of Danish Society of Clinical Microbiology.

## Supplementary material

**Supplementary material** is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as **Supplementary data**.

**Consent:** The authors confirm that written informed consent for publication of this case report including images had been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

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