Case Report

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Rat Bite Fever: A Case Report Review

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ABSTRACT

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Background

Streptobacillus moniliformis, a common representative of the nasopharyngeal flora of rodents, is the causative agent of the zoonosis rat bite fever. The clinical presentation with fever, migratory polyarthralgias and skin rash may establish a challenging differential diagnosis. The zoonosis has a potentially lethal course in a vulnerable population (children, low socioeconomic class) and a commonly available treatment (penicillin). The goal of this case report review is to outline common epidemiological factors and clinical presentation forms in order to increase clinical awareness and install fast antimicrobial treatment.

Case Description

An 11-year-old girl is referred to the emergency department by her general practitioner because of a recurrent fever in the last two weeks, painful, swollen joints (left shoulder, elbow, knee and finger) and a fluctuating rash on the face and limbs. There are accompanying complaints of general malaise (earache, sore throat, reduced intake with one-time vomiting and diarrhea). The child's medical history reports ADHD for which she is being treated with methylphenidate. The other family members are in good health and the travel history is negative. A tick bite was not noticed. At the time of clinical examination, the child is in good general condition with fever up to 39.0 °C. The examination confirms a mild pharyngitis with accompanying bilateral cervical adenopathies and a mild swelling of the proximal interphalangeal joint at the level of the left middle finger. There are no visable skin defects or splenomegaly [1-5]. A peripheral blood sample shows mild leucocytosis (12 700/mm^3) with absolute neutrophilia (10 130/mm^3) and a minimal CRP increase (8.6mg/dl). Investigation with chest X-ray, urine sediment and culture and SARS-COV-2 and influenzae PCR all remain negative. Ultrasound investigation of the swollen proximal interphalangeal joint shows increased intra-articular fluid.

The girl is admitted to the pediatric ward for conservative management with fluid and antipyretic treatment. An infection of viral origin (Enterovirus, Parvovirus B19, Epstein-Barr virus) is suspected. Twenty hours after incubation, growth is detected in a pediatric blood culture bottle (Peds Plus Bactec BD). The gram stain shows filamentous gram-negative bacilli. Gray, small, shiny colonies appeared on blood agar after overnight incubation in 5% CO_2 at 37 °C. Identification with MALDI-TOF-MS results in Streptobacillus moniliformis. Antimicrobial susceptibility testing was unsuccessful (no bacterial growth). The girl was treated with a two-week amoxicillin therapy, initially intravenously. After favorable clinical and biochemical evolution, she was further treated at home with amoxicillin per os. Reconstitutio ad integrim occurred. Only after thorough anamnesis it became clear that the child got bitten by her father's pet rat two weeks before admission [6-10].

Methods

A search was conducted in the PubMed database using the terms 'rat bite fever', '*Streptobacillus moniliformis*', '*streptobacillosis*' and 'epidemic arthritic erythema' combined by the Boolean operator 'OR'. This resulted in 101 hits. Inclusion criteria were case report, English or Dutch language, Europe, free full text article available and relevance to the subject. The following data were extracted from the 20 remaining case reports: age, area, rat exposition,

incubation period, symptoms on day of admission, (duration of) antibiotic treatment, outcome.

Results

In 11 out of 18 case reports, direct rat contact occurred in a domestic setting (direct contact with pet rats in nine cases and in precarious house conditions in two cases). Rat exposure was occasional in seven out of 18 case reports. Probably rat manipulation using gloves in an occupational setting makes transmission of Streptobacillus moniliformis less likely. In four cases, the index patient was a child. The time frame between direct rat contact (direct contact with rat excretions, rat bite or rooster scratch) and hospital admission varied between five and 21 days in nine cases. It is clear that a bite or scratch mark might not be visible anymore on the day of admission. The majority of cases presented with fever (17/20) and polyarthritis or polyarthralgia (15/20). A rash was described in 8/20 cases. Five cases had a complicated course (endocarditis, spondylodiscitis, osteomyelitis, peripheral ischemia). In the majority of cases, an infectious syndrome was suspected in the presence of fever and markedly increased inflammatory parameters [11-15].

Here blood sampling was performed, and antibiotic therapy was initiated empirically. However, in case five, there was a significant delay in the start of antibiotic therapy. Benzylpenicillin administration was started only seven days after hospital admission which resulted in gradual recovery and persistent damage to the right wrist and left-hand extensor tendons. This case presented with polyarthritis, and the patient was initially treated with corticosteroids and colchicine as the presumed diagnosis was median vessel vasculitis and gout respectively. In our case and in case 18, antibiotic therapy was only initiated after growth detection in blood cultures taken on admission. Gram stains showed gram-negative rods. This underlines the importance of blood culture sampling even in suspicion of a viral origin of fever. A neutrophilic formula and an elevated procalcitonin point in the direction of a bacterial origin. Laboratory diagnosis relies on the culturing of blood, purulent or synovial fluid or on 16S rDNA testing of suitable specimens. Ten blood cultures and 10 alternative cultures (synovial fluid, abcess fluid, aortic valve, blister fluid, and peroperative samples) yielded growth. In 11 cases, 16S rDNA was used in the diagnostic workup.Administration of various classes of antibiotics (B-lactams, cephalosporins macrolides) resulted in complete resolution. In 19 cases, hospital admission was necessary. Nineteen patients recovered and one patient died (Table 1) [16-19].

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Table 1.

PMID	Age	Area	Rat Exposure, Route of inoculation, Incubation period	Diagnostics	Prodromi	Clinical Features And Complications	Biochemistry	Differential Diagnosis	Treatment Regimen	Hospital Admission	Outcome
11484516 (2001) (1) 114 11484516 (2001) (1) 84516 (2001) (1)	16	BE	-Bite of a pet rat a few days before admission	Blood cultures: growth after 72h of incubation >Gram stain: pleomorphic, filamentous and branching, non-motile Gram-negative bacilli with swellings >Culture: positive >Identification (phenotypically and gaschromatographically): *Streptobacillus moniliformis*	-minus D1: -recurrent vomiting -headache	D0: -fever -headache -recurrent vomiting		*meningitis *urinary tract infection	amoxicillin-clavulanate IV (3 days) and PO (10 days) (4x 500mg)	yes	CR
11757440 (2001) (2)11757440 (2001) (2) 011757440 (2001) (2) 11757440 (2001) (2)11757440	48	NO	-Bite by pet rat, 10 days before hospital admission	Blood cultures: >Culture positive: *Streptobacillus moniliformis*		-minus D5: fever + malaise -minus D3: rash and arthritis hand and feet D0: hospital admission	CRP: 231 md/dl ESR: 88/hour aspartate aminotransferase: 87U/L alanine aminotransferase 218 U/L gamma-GT 461 U/L		Erythromycin > 2 weeks IV penicillin	yes	CR
11518380 (20 11518380 (2001) (3) 01) (3)	13	UK	-rat bite on the fingertip 5 days before the onset of symptoms in a pet shop	Right hip joint effusion (arthrotomy and joint lavage) >seropurulent material >Gram stain: Gram-negative bacilli >culture: *Streptobacillus moniliformis* (using special culture media) sensitive to penicillin	-minus D9: malaise and fluctuating arthralgia affecting the right hip	D0: -progressive worsening of right hip pain and inability to bear weight -initially apyrexial, 39°C a few hours after admission	L: normal ESR: >100/hour CRP: 69 mg/L		IV penicillin > oral amoxycillin (6 weeks)	yes	CR

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12922949 (2003) 12922949 (2003) (4) (4)	62	UK	-minus D21: rat bite on left foot	right knee aspiration: >purulent >neutrophilic formula >Gram stain: regular Gram negative intracellular bacilli >culture: positive (small grey colonies) >Gram stain colonies: filamentous cells with many bulbous swellings, typical of *Streptobacillus moniliformis* Blood cultures: negative TTE: negative	-minus D17: pain over his left foot followed by pain and swelling in both knees, elbows, wrists, the small joints of both hands, and the left ankle	D0: -febrile -jaundice -synovitis affecting the wrists, interphalangeal and metacarpophalangeal joints of the hands, effusions in the right knee, right ankle, and left midtarsal joint	L: 29.3×10^9/L with 90% PMN CRP: 197 mg/l Liver function tests: cholestatic hepatitis serum bilirubin 55 µmol/l alkaline phosphatase 399 U/l alanine aminotransferase 230 U/l aspartate aminotransferase 63 U/l Hepatitis B and C serology: negative	-sepsis -hepatitis -streptobacillary septic arthritis	Oral ciprofloxacin and doxycycline (history suggestive of type I hypersensitivity to penicillin) > high dose IV penicillin G 18 MU during 4 weeks (skin tests to penicillin G: negative)	y	CR

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12810419 (2003) 12810419 (2003) (5) (5)	56	UK	-rat bite in the web space of the index and middle finger of the right hand 3 weeks before admission	left ankle aspirate: >urate crystals left thumb MCP joint aspirate: >Gram stain: "odd" Gram positive coccus >culture: Gram negative pleomorphic coccobacillus *Streptobacillus moniliformis* (confirmed by DNA sequencing)	-10D: fevers, cough, sore throat, and loose stools -8D: acute polyarthritis affecting the right wrist, left thumb, both feet, and the right ankle, followed by arash over elbows, fingers, and feet	-Apyrexal -maculopapular, nonblanching rash with pustules and necrosis over the extensor surfaces of both elbows and left calf -acute, erythematous synovitis affecting the right elbow, wrist, and shoulder, left thumb MCP joint, both mid-tarsal joints, and right ankle -healing lesion in the web space of the index and middle finger of the right hand Complications: >Critical ischaemia on his right hand from the mid-palm distally >Pyrexia >Acute worsening of his joint symptoms (left ankle and thumb) Diagnosis: rat bite fever complicated by polyarticular gout	L: 12.6*10^9/l neutrophils: 11.4*10^9/l CRP: 225mg/l ESR: 79 mm/1st hour	-reactive arthritis -vasculitis	methylprednisolone and cyclophosphamide (presumed medium vessel vasculitis) Colchicine (gout) IV benzylpenicillin and flucloxacillin > 6 weeks oral doxycycline	yes	gradual recovery, with persistent damage to the right wrist and left hand extensor tendons

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18562588 (2005) 18562588 (2005) (6) (6)			-shaking chills and back pain, a few days after a rooster scratch on his left hand	-Blood cultures: positive >3 anaerobic bottles >2 aerobic bottles > gram stain: pleomorphic forms with fusiform gram-negative rods > culture: positive > identification by conventional biochemical and carbohydrate analysis: failed > identification by 16S rRNA sequencing from agar cultures: failed Aspiration of the abscess: > Gram stain: pleomorphic fusiform gram-negative rods > Culture: negative > 16S rRNA PCR assay: obtained 450-kb amplicon shared 99% homology with that of the 16S rRNA gene of *Streptobacillus moniliformis* Pericardial and pleural effusions and collections in the right iliac psoas in contact with a screw of the right prosthesis > Culture: negative	-minusD7: shaking chills without fever and back pain that irradiated to both legs, which gradually disappeared	Medical history: -bilateral total hip replacement D0: -deterioration of general health -inflammatory syndrome Complications: -psoas abscess and spondylodiscitis at T5 and T6 and at L2 and L3	L: 19 x 10^9/L with 18 x 10^9/L neutrophils CRP: 488 mg/L Procalcitonin: 13 ng/ml (<0.5 ng/ml)	-Sepsis -Cauda equina syndrome -lumbar hernia -Spondylodiscitis -Malignancy	IV amoxicillin-clavulanic acid 3*1g + ofloxacin 2*200 mg > imipenem – cilastatin 2*1g + ciprofloxacin 2*400 mg + teicoplanin 1*600 mg > 9 week treatment with IV ofloxacin 2*200 mg + clindamycin 3*600 mg + metronidazole 3*500 mg	yes	CR
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16186643 (2005) (7 16186643 (2005) (7))	23	NL	-nine pet rats -an assistant at a veterinary clinic -no overt bite	Blood cultures: >Gram stain: gram-negative rods >Culture: *Streptobacillus moniliformis* A PCR for *Streptobacillus moniliformis* using the saliva of the pet rats: positive	-malaise for several weeks - painful and swollen joints (knees and wrists most prominently) - a large red lesion on the right upper arm, which had resolved spontaneously - painful, small, red spots on her hands and feet with especially the palmar side of the hands and fingers affected	D0: - fever accompanied by rigors - slight swelling of the left wrist, with diminished flexion - a maculopapular rash with numerous small, dark-red eruptions, some of which with a blister-like appearance on both hands and feet - a small aphthous lesion on lateral edge of the tongue	CRP: 22 mg/l	- systemic lupus erythematosus - Henoch-Schonlein purpura - cytomegaly/ Epstein-Barr virus infection - toxic drug reaction - secondary syphilis	Treatment with oral clarithromycin	yes	CR

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16254115 (2005) 16254115 (2005) (8) (8)	7	FR	-two pet rats and direct contact with rats' faeces	Blood cultures: negative Cerebrospinal fluid cultures: negative Blister fluid samples: >Gram stain: pleomorphic Gram negative rods >culture positive >Biochemical identification: unsuccessful >Antimicrobial susceptibility testing: unsuccesfull >bacterial 16S ribosomal DNA PCR: 99% similarity with the Genbank *Streptobacillus moniliformis* sequence Z35305 (type strain ATCC16467)		D0: -fever -bilateral arthralgia in the knees, ankles, elbows, and wrists -maculopapular morbilliform exanthema on the palms and soles, associated with several blisters (3–8 mm in diameter), containing a whitish fluid, on the face and elbows D5: -bilateral desquamation of the fingers and toes	L: normal CRP: 300 mg/L ESR: 60 mm/hour	-atypical Kawasaki disease -toxic shock syndrom	Erythromycin (7 days) and amoxicillin (15 days)	yes	CR
18023687 (2007) (9) 18023687 (2007) (9)	29	GE	-right hand injury 2 weeks before admission	Aortic valve: > Gram stain: Gram-positive/Gram-variable straight, curved, and filamentous rods > Culture: tiny colonies on blood sheep agar, showing long filamentous Gram-variable rods >Identification: 16S rRNA gene sequencing: *Streptobacillus moniliformis* Blood cultures: negative	Right hand injury with progressive lethargy and weakness	D0: Fever, dyspnea, dizziness, increasing somnolence Complication: Endocarditis with giant floating vegetations on a degenerated, insufficient aortic valve and a large perivalvular abscess cavity		-Sepsis	empirical antibiotic therapy: ampicillin, ceftriaxone, and gentamicin > penicillin, fosfomycin, and gentamicin	Yes	Almost normal left and right ventricular function with a well-functioning aortic valve prosthesis on echocardiography

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22180758 (2009) (10)	23	UK	manipulation of a dead rat two weeks before his illness	blood cultures: culture: weak growth of a Gram variable rod PCR: *Streptobacillus moniliformis*		D0: - swinging pyrexia, rigors - headache - abdominal pain, vomiting with right upper quadrant tenderness - right shoulder pain with unremarkable examination - no rashes	L: 12×10^9 cells/L CRP: 333 mg/L alkaline phosphatase 130 IU/l (NR 45–120 IU/L), aspartate transaminase 278 IU/l (NR 0–40 IU/l), alanine transaminase 339 IU/l (NR 0–40 IU/l), γ-glutamyltransferase 210 IU/l (NR 11–50 IU/l)	Atypical Pneumonia Urinary tract infection	oral amoxicillin/clavulanic acid and erythromycin	yes	CR
21292904 (2011) (11) 21292904 (2011) (11)	89	FR	-living alone in precarious conditions in contact with rats	Blood cultures: >1 anaërobic bottle: growth detection >gram stain: pleomorphic filaments and branching Gram-negative bacilli.		D0: foot burns (domestic accident) D4: fever, somnolence		-Sepsis	Amoxicillin-clavulanate and gentamicin>D9: ceftazidime, vancomicin, and metronidazole>D11: rifampicine	yes	Died on day 14

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				>Culture: negative >16S-rRNA gene amplification PCR assay followed by sequencing: *Streptobacillus. moniliformis* -Centrifugation shell vial technique: inoculation of previously frozen blood culture broth sample on Colombia blood agar (bioMerieux) and ECV 304 human endothelial cell monolayers: after 24 hours, a cytopathic effect was observed on the monolayer cells shell vial super- natant: >Gimenez and gram staining: Gram-negative bacillus inoculated onto Colombia blood agar and new shell vials: both positive. bacterial identity was verified again by 16S rRNA gene sequencing					and doxycyclin		
22744925 (2012) (12) 22744925 (2012) (12)	55	NL	-rat breeding to feed pet snakes with regular rat bites	Left thenar eminence pus culture: > Gram stain: pleomorphic Gram-negative bacillus > S16 rRNA sequencing: *Streptobacillus moniliformis*	-MinusD4: fever with headaches, myalgia and neck pain	D0: -subfebrillitas - nausea - red spotted non-blanchable maculopapular rash on both palms and soles joint - pain of the wrists and fingers with enlarged and painful left thenar eminence	L: 8.6 x 10^9/l CRP: 235 mg/l	-Leprospirosis, -Parvovirus B19 -Coxackievirus - Enterovirus - Syphilis	Oral doxycyclin	No	CR

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25414213 (2014) (13) 25414213 (2014) (13)	49	UK	-homeless man -no overt animal bites or rodent contact -contaminated food products?	Positive blood cultures: > Direct Gram stains: long and thin filamentous gram-negative rods in loops and coils >Culture: Small grey–white colonies > MALDI-TOF MS: S. moniliformis (ID scores of 1.8 and 2.1) >16S ribosomal RNA (rRNA) gene detection and sequencing: S. moniliformis > susceptibility testing: unsuccessful		- septic with high-grade fever (40°C) - progressively worsening right leg pain, swelling and rash -apical pan-systolic murmur -splinter hemorrhages -TTE and TEE: vegetation on mitral valve -splenic infarcts secondary to probable septic emboli Infective endocarditis	L: normal CRP: 117 mg/L normocytic normochromic anemia	cellulitis with deep vein thrombosis occult abscesses (chest, abdomen, pelvis)	IV benzylpenicillin and flucloxacillin > co-amoxiclav and gentamicin > meropenem and doxycycline > IV high-dose benzylpenicillin 6*2.4 g and oral doxycycline 2*100 mg (6 weeks)	yes	CR after mitral valve replacement
24695665 (2014) (14) 24695665 (2014) (14)	29	UK	-direct contact with multiple pet rats	Blood cultures: negative Right ankle joint aspiration >purulent >microscopy: no organisms >culture: no growth on culture >bacterial 16S rRNA PCR: negative. Repeat right ankle aspirate: >bacterial 16S rRNA PCR: positive for the 16S rRNA gene, diagnostic for *Streptobacillus moniliformis* infection	-minus D5: worsening generalized malaise, fever, sore throat and polyarthralgia	D0: - malaise - fever - sore throat - polyarthralgia - bilateral plantopalmar rash (widespread, partially blanching, rash with vesicular, petechial and pustular components over both feet, hands, legs and buttocks)	L: 10.62×10^9 cells/L CRP: 211 mg/L ESR: 36 mm/h (normal <14 mm/h)	Vasculitis Viral exanthematous pustulosis	empirical broad-spectrum antibiotics>IV benzylpenicillin (2 weeks)> oral amoxicillin (3 weeks) and physiotherapy	yes	CR (minimal pain on impact activities)

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28652481 (2017) (15 28652481 (2017) (15))	44	UK	-purchase of live rats to feed pet snakes -no overt rat bites or scratches -direct contact of bare hands with rat and snake faeces two days before onset of systemic symptoms	-Blood cultures: negative -Aspiration of right knee effusion >purulent >neutrophilic formula >Gram stain: pleomorphic, filamentous, gram-negative rods arranged in chains and tangles >culture: positive for *Streptobacillus moniliformis*	-minus D14: acute malaise, headache, myalgias, subjective fevers, vomiting and diarrhea with resolution	Medical history: -mild psoriasis -bilateral ankle fractures -right metacarpal fracture -right knee anterior cruciate ligament repair D0: -subfebrillitas -swelling of ankles and right knee, hand, wrist and shoulder -large right knee effusion -no rashes	L: 10.3 × 10^9/L CRP: 340 mg/L	-Septic arthritis -Sero-negative inflammatory arthritis (spondyloarthritis) -Rheumatoid arthritis -Crystal related arthritis -Sarcoidosis	IV cefazolin (2 days) > IV penicillin G 6*2 MU (2 weeks) > IV ceftriaxone 2g (2weeks)	yes	- Extension of therapy with 2 because of persistent mild wrist pain at completion of the course of IV penicillin G - CR
28322713 (2017) (16) 28322713 (2017) (16)	59	FR			-15-day history of fever and arthralgia (left knee, right wrist) but no signs of rash	unable to stand had acute progressive onset of dyspnea	L: 15 × 10^9/L, predominantly neutrophils, CRP: 125 mg/L			Yes, IC	
31859955 (2019) (17) 31859955 (2019) (17)	76	PT	rat bite	lumbar puncture: normal CSF CT scan: normal Blood cultures: positive Identification by PCR and Sanger sequencing targeting bacterial 16S rRNA: *Streptobacillus moniliformis* TEE negative Magnetic resonance imaging (MRI) with T2-weighted images: high signal intensity in the C5, C6, and C7 vertebrae with meningeal enhancement and the left sternoclavicular joint.	medical history: cervical degenerative disc disease	D0: -four-day history of fever, prostration, myalgias, and headache -subfebrile, hypotensive, incised wounds on two fingers of her left hand -neck stiffness D3: worsening neck pain and tetraparesis Diagnosis: vertebral osteomyelitis and septic arthritis associated with rat bite fever	L: 14,670/μL (86.3% neutrophils) CRP: 334 mg/dL		IV ceftriaxone 2 g (26 days) > oral amoxicillin-clavulanate (eight months) after hospital discharge	yes	CR

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32998485 (2020) 32998485 (2020) (18) (18)	20	No	-scratches from pet rats a few days before start of illness -worked as a nurse in a veterinary clinic	Blood cultures: >culture: gram-negative rods >identification using MALDI- TOF MS: *Streptobacillus moniliformis*	-couple of episodes of chills in the days prior to admission to the hospital	D0: 3-to-4-day history of fever, headache, dizziness, nausea and a maculopapular exanthema on her arms and palms of her hands	L: 13 · 10^9/L (normal differential count) CRP: 222 mg/l	viral syndrome	IV cefotaxime 3 x 2g (3 days) > IV ceftriaxone 1 x 1g (4days) > PO therapy phenoxymethylpenicillin 4 x 1g (7 days)	yes	CR
32117690 (2020) (19) 32117690 (2020) (19)	66	UK	-minus D8: bite by a small rodent on her right thumb, brought into the home by her cat	Blood cultures: negative Joint aspirate and arthroscopic washout: negative operative tissue samples (two-stage revision) >16S PCR: *Streptobacillus moniliformis*		Medical history: osteoarthritis: 2011: right unicondylar knee replacement 2014: right total knee replacement D0: -progressive thumb inflammation -acute-onset right knee inflammation -self-discharge D2: Re-admission - progressive deterioration of her right knee, unable to weightbear -pyrexia, sweating and intermittent rigors - erythematous and tensely swollen thumb with development of a soft tissue abscess - right prosthetic knee was hot, with a moderate effusion and severe generalised tenderness Complications: sepsis, delirium	L: 19.2 x10^9/L CRP: 353 mg/L	-Surinfected bite wound -sepsis -prosthetic joint infection	IV vancomycin and doxycycline>meropenem (6weeks) (type-1 hypersensitivity to penicillin-based antibiotics)	yes	CR after two-stage knee revision

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Roe-selare (2020) (20) Roe-selare (2020) (20)	11	BE	-bite of a pet rat	Blood cultures: positive (MALDI-TOF)	-minus D14: recurrent fevers -polyarthritis (left shoul-der, ellbow, knee and finger) -fluctuating rash on trunck and limbs	D0: -fever -polyarthritis -rash	L: 12 700/mm^3 with 10 130/mm^3 neutrophils CRP: 8,6 mg/dl	-infectious syndome: -Enterovirus -Parvovirus B19 -EBV -Brucella	amoxicillin (4*1g) for 2 weeks	yes	CR

Conclusion

Rat bite fever is strongly underdiagnosed from both a clinical and a microbiological point of view. It is recommended to include rat bite fever in the differential diagnosis in the presence of a fever syndrome of unknown origin and anamnestic confirmed rat exposure. This diagnosis becomes more likely if polyarthralgia and rash are present simultaneously. In case of a clinical suspicion of rat bite fever the microbiology, department should be consulted and a bacterial 16S ribosomal DNA PCR should be conducted when necessary. Since most transmissions occur in a domestic setting, keeping rats as pets cannot be recommended.

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