RAT BITE FEVER: COMPLICATIONS, TREATMENT AND PROFESSIONAL NURSE ROLE IN COLLABORATION WITH DOCTORS FOR PATIENT SAFETY

By

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Abstract

Rat-bite fever, also known as streptobacillosis, spirillary fever, bogger, and epidemic arthritic erythema, is a zoonotic illness that manifests with acute relapsing fever with migratory polyarthralgia. It is a zoonotic infectious disease from rodents to man either via rodent urine or mucosal secretions or even nasal, fecal, or ocular secretions of an infected rodent. It was reported in Japan, the United States, Europe, Australia, and Africa caused by two different bacteria: *Streptobacillus moniliformis*, the only bacteria that causes RBF in North America (streptobacillary RBF) *Spirillum minus*, common in Asia (spirillary RBF, or sodoku). Without treatment, rat bite fever can lead to severe complications; pneumonia, meningitis, heart infection (myocarditis, endocarditis) and blood sepsis, led to death 7-10%. When treated promptly, prognosis is very good. Tetanus and rabies immunization is a must, although rat bite rarely causes rabies.

Key words: Rat, Fever, Bacteria, Complications, Treatment, Nursing role

Introduction

Rat-bite fever (RBF, or Haverhill fever), is also called Spirillary Rat-Bite fever or Sodoku, relapsing infection type and transmitted to humans by the bite of an infected rat affecting all ages and both sexes. A rarely diagnosed, systemic illness caused by either *Streptobacillus moniliformis* or *Spirillum minus*. *S. moniliformis* causes most cases of disease in the USA; *S. minus* causes RBF in Asia, but also reported worldwide (Grude *et al,* 2001), But, as RBF is a nationally unreported disease, and responded to empiric antibiotic therapy without diagnosis, its actual incidence was unknown (Torres *et al,* 2003). Also, the saliva of some rats' species carries hazardous diseases, such as leptospirosis and orthohantaviruses or hanta-virus (Meyer and Schmaljohn, 2000).

Epidemiology: *S. moniliformis* is found in nasal and oropharyngeal flora of rats and perhaps other rodents, with nasopharyngeal carriage of *S. moniliformis* by healthy laboratory rats varied between 10 &100% (Anderson *et al,* 1983). Bhatt and Mirza (1992) in Kenya reported a 17 year old male suffered from rat bite fever after a bite of domestic rat, who recovered completely after a course of penicillin and gentamicin.

Human infection can result from a bite or scratch from an infected or colonized rat, handling of infected rat, or ingestion of food or water contaminated with infected rat feces (CDC, 2005). Valverde *et al.* (2002) in USA reported that RBF is a zoonotic and non-reportable disease. They found natural RBF infection in 2 monkeys; a rhesus macaque (*Macaca mullata*) with valvular endocarditis, and a titi monkey (*Callicebus* sp.) with septic arthritis. Abdulaziz *et al.* (2006) in Canada reported that Haverhill fever & RBF are closely-related syndromes caused by *S. moniliformis* characterized by an abrupt onset of fever with rigors, myalgias, headache, polyarthritis, and rash. They detected an acute polyarthritis patient with spine involvement. Elliott (2007) in USA reported that RBF caused by *S. moniliformis* is a systemic illness characterized by fever, rigors, and polyarthralgias. He added that also *S. fusobacteriales* causes streptobacillary rat bite fever and Haverhill fever and increasing rats'

popularity and other rodents as pets, together with invasive risk or fatal disease, needed more attention to this infectious RBF. Gaastra *et al.* (2009) in Holland added that RBF causative agent was found in squirrels, ferrets, dogs, and pigs. Madhubashini *et al.* (2013) in India reported a native mitral valve endocarditis in a 44-year-old male patient caused by *S. moniliformis* diagnosed by transesophageal echocardiography & blood culture. Eisenberg *et al.* (2016) in Germany reported that despite published case reports, RBF diagnosis continues to be a diagnostic dilemma, as the mostly applied 16S rRNA sequence analysis may be uncertain for proper pathogen identification. They added that virtual was unknown as to prevalence in man, and animals, and for real assessment of pathogen's spread, epidemiology and virulence traits must focus on *Streptobacillus* genomic background. Michel *et al.* (2018) in Germany added that RBF is an unreported, undiagnosed worldwide emerging zoonosis and that *Spirillum minus* & *S. moniliformis* was the major causative agents usually colonies rats without clinical signs. A group of house or domestic rats (*Rattus rattus*) kept in a zoo exhibition for educational purposes suffered from neurological signs; disorientation, torticollis, stall walking, ataxia and death. The general paucity of *Streptobacillus* isolates, especially from their respective animal hosts, precludes definitive proof of host tropisms. They added that it was the first report of *S. notomytis* outside Asia and Australia and the first evidence for its role as a facultative pathogen in the domestic *R. rattus*. Ogawa *et al.* (2018) in Japan by using nested PCR identified an indoor case of RBF in a 94-year-old woman with *S. notomytis*.

Crofton *et al.* (2020) in USA reported a pregnant woman sought care for right leg pain, fevers, left upper quadrant pain, generalized weakness, fatigue, and inability to bear weight on her right leg, which pregnancy was complicated by hyperemesis and weight loss. Her pets included a rescued wild bird, a cat, and four rats, and she recalled multiple cat bites and scratches since child-hood, but denied injection drug use. They added that RBF diagnosis was delayed due to symptoms of a concomitant pregnancy. Julius *et al.* (2021) in South Africa reported that RBF was a global zoonosis with a mortality rate of up to 13% without treatment. They added that presence of multiple invasive *Rattus* sp. with high densities in urban, informal human settlements and increased rat bites cases, phylogenetic analysis of 4 gene regions (16S rRNA, *gyrB*, *groEL*, & *recA*) identified 2 discrete lineages *S. moniliformis* were exclusively in *R. norvegicus* and *S. notomytis* retricted to 2 species of *R. rattus* complex.

Transmission: Contamination of food and water with *S. moniliformis* caused several outbreaks of RBF and in 1926, 86 persons in Haverhill, Massachusetts, developed a febrile illness (Haverhill fever) after consumption of infected unpasteurized milk (Place and Sutton, 1934). An outbreak among 304 school children was caused by water contaminated with rat excretions (McEvoy *et al*, 1987). About 30% patients were not bitten or scratched by a rat; risk for RBF included handling and nosocomial as laboratories or pet stores (CDC, 1998). Vetter *et al.* (2016) in USA reported RBF infection from a kiss.

Microbiology: *S. moniliformis* and *S. minus* are pleomorphic fastidious branching Gram negative bacilli. They stain irregularly and can be mistaken for Gram positive pleomorphic rods. Bacteria are aerobic, facultatively anaerobic, and require specific media for isolation (10 to 20% serum) and incubation in a 5 to 10% CO_2 environment.

S. moniliformis grows slowly. So, cultures should be held for at least five days to allow identification. On solid agar plates, pinpoint colonies representing cell wall-defective variants (L-forms) may surround larger gray-white colonies, and inoculation into thioglycolate broth enriched with serum produces growth in typical "puff-ball" colonies (Pins *et al*, 1996). *S. moniliformis* was identified by a fatty acid profile on gas chromatography, but in contrast, biochemical testing was

difficult and not accurate due to the organism fastidious nature (Rowbotham, 1983).

Clinical pictures: The symptoms of RBF caused by *S. moniliformis* start abruptly two to ten days following exposure with fever, myalgias, arthralgias, vomiting, and headache (CDC, 1984). Fever is often irregularly relapsing. The initial symptoms are followed by a maculopapular rash on the extremities (Stehle *et al*, 2003), followed by polyarthritis up to 50% of patients (Mandel, 1985).

Rash was typically seen on the extensor surface of the extremities and may involve palms and soles, but usually maculopapular, it could be petechial, purpuric, or pustular (Tandon *et al*, 2006). But, RBF caused by S. minus has a longer incubation period (1 to 3 weeks), and the initial wound may reappear at the onset of the systemic illness or persist with edema and ulceration. Arthritis is not a common clinical finding. The infection can be rapidly fatal both in children and adults (McHugh *et al*, 1985). Two cases of fulminant sepsis and death in previously healthy men occurred in the United States, one after a rat bite in a pet store and second most likely from a sick pet rat (Sens *et al*, 1989).

Complications: Reported in Chelmsford and Haverhill outbreaks included: 1- Chelmsford, four patients with moderately severe symptoms had bacteremia, without more complications (Shanson *et al*, 1983). 2- Haverhill, eleven of 17 patients had positive blood cultures; two patients developed fatal pneumonia (Shvartsblat *et al*, 2004). CDC (2019) added that complications of streptobacillary RBF can also include: a- Abscesses (pockets of infected fluid) inside body, like in belly (abdominal cavity), b- Infections of liver (hepatitis) and kidneys (nephritis), c- Infections of lung (pneumonia), d- Infections of brain and central nervous system (meningitis), e- Infections involving heart (endocarditis, myocarditis, or pericarditis). CDC added that symptoms and signs of spirillary RBF (sodoku) can vary and often include: a- Fever that may come and go or occur repeatedly, b- Swelling or formation of the

ulcer at bite wound (if present), c- Swollen lymph nodes (small glands that filter lymph, the clear fluid that circulates via lymphatic system, and help fight infections), and d- Rash (about 5 of 10 people with sodoku) that can appear all over the body or only near bite wound area (if present)

Most serious invasive infections appeared as case reports, and include meningitis, endocarditis (Rordorf *et al*, 2000), included prosthetic valve endocarditis, myocarditis, pneumonia, focal abscesses (Chen *et al*, 2007), bacteremia, septic arthritis, multiple organs failure, pneumonitis, liver abscess, and adrenal gland failure (Wang and Wong, 2007), and rheumatoid arthritis (Akter *et al*, 2016).

Diagnosis: Classically, RBF diagnosis was based on bacterial cultures. But, this was difficult in routine practice, because *S. moniliformis* is a fastidious gram-negative bacillus that needs special media and environments for isolation (Lambe *et al*, 1973).

RBF must be suspected in patients with fever, nausea, vomiting, joint pain, and rash, as well as a known or suspected history of rodent exposure. Clinicians should consider RBF in differential diagnosis of an unexplained febrile illness or sepsis in patients reporting rat exposure especially if the fever pattern was relapsing or intermittent, a maculopapular rash was present, and/or the patient with an asymmetrical polyarthritis (Dendle *et al*, 2006). Kämmerer *et al.* (2021) in Germany reported a female patient presented with painful hemorrhagic pustules and purpuric lesions on hands and feet that developed fever and migratory polyarthralgia, and owned rats and handled contaminated rat feces and urine. They added that difficulties in clinical and microbiological diagnosis highlight the need for a thorough and complete history-taking and a greater understanding of this rare infectious disease.

Blood or synovial fluid collected in tubes without sodium polyanethol sulfonate, an anticoagulant that can inhibit growth of the organism must be cultured. Microbiology laboratory must be alerted to the suspicion of

RBF so that specific media and culture conditions were used to optimize organism isolation (Zhang *et al,* 2019). But, the laboratory must be incubated blood cultures for 21 days, if serologic test was not available.

Molecular techniques, such as PCR assisted RBF diagnosis, but was not available to most practitioners, which showed a quick, accurate diagnosis (Boot *et al,* 2002).

Differential diagnosis (Washburn, 2015): RBF must be differentiated from 1- Meningococcemia, 2- Disseminated gonorrhea, 3- Lyme disease, 4- Brucellosis, 5-Herlichiosis, and 6- Rickettsial infections (Woods, 2013). Also, must include streptobacillary RBF and Haverhill fever and several bacterial, parasitic and viral infections diseases as, leptospirosis, Rocky Mountain spotted fever, malaria, babesiosis, typhoid fever; *S. pyogenes* & *S. pyogenes*-associated diseases, *S. aureus* infection, viral exanthems, secondary syphilis, Epstein-Barr virus, and/or coxsackieviruses (Freels and Elliott, 2004). Moreover, RBF must be differentiated from arthropod dermatitis or insect bites (Morsy, 2012) and skeeter syndrome (Abdel-Motagaly *et al,* 2017), as well as allergic reactions caused the ants (Sanad *et al,* 2002) or by hymenopterous stinging insects (Abdelrahman *et al,* 2015).

Besides, RBF must be differentiated from non-infectious causes as collagen vascular diseases and drug reactions (Taber and Feigin, 1979), often misdiagnosed by clinicians tha led to lingering symptoms and worsening risks in patients; left untreated mortality rate of 13% (Dendle *et al,* 2006).

Treatment: The case-fatality rate was up to 25% in untreated cases mainly infants. Treatment of RBF associated with an animal bite must begin with appropriate management of bite wound (Carbeck *et al,* 1967). This incuded copious irrigation of wounds and determination need for tetanus or rabies post-exposure prophylaxis (Ojukwu and Christy, 2002). CDC (2019) reported that there was limited research on the effectiveness of the specific antibiotics to treat RBF. But, *S. moniliformis* is generally susceptible to sev-

eral antibiotics: 1- Penicillin, 2- Cephalosporins, 3- Carbapenems, 4- Aztreonam, 5- Clindamycin, 6- Erythromycin, 7- Nitrofurantoin, 8- Bacitracin, 9- Doxycycline, 10- Tetracycline, 11- Teicoplanin, and/or 12- Vancomycin. They added that IV penicillin G given for seven or more days, followed by oral penicillin was recommended. But, the patients may develop Jarisch-Herxheimer reactions due to penicillin treatment that usually improve quickly once antibiotics started. However, without the appropriate treatment, the mortality rate was about 10%. A patient allergic to penicillin, doxycycline or streptomycin was alternative choices. Other groups at increased risk were patients over 65 years old, or with weakened immune systems (cancer, HIV/AIDS, organ implants or those on certain medications as steroids (CDC, 2018).

Rat-bite fever is a zoonotic disease can be directly transmitted by domestic and wild rats, gerbils, and mice to humans Also, house-pets such as dogs or cats exposed to these animals can also carry the disease and infect humans (Adam *et al,* 2014). Eisenberg *et al.* (2017) in Germany added that snakes that eat rats might serve, at least temporarily, as reservoirs for human infection. Wouters *et al.* (2008) in the Netherlands reported that rat bite fever caused by the bite of a dog or cat was very seldom documented and added that swabs taken from the mouth of 18 dogs with proven contacts with rats showed *S. moniliformis* DNA by PCR. Meanwhile, rats and other small rodents are almost never infected with rabies, without transmission to a human from one of these animals. If animal was not available for testing, post-exposure prophylaxis for bites must be considered individually in consultation with health authorities (Raffin and Freemark, 1979). But, the CDC (2021) in USA reported that raccoons, skunks, and foxes are the terrestrial animals most often infected with rabies, and that bites by such wildlife must be considered a possible exposure to the rabies virus.

In vitro, *S. moniliformis* is usually sensitive to penicillin, ampicillin, cefotaxime, azit-

hromycin, and doxycycline; but resistant to polymyxin B, gentamicin, tobramycin, ciprofloxacin, and levofloxacin (Taber and Feigin, 1979). Strains varied in sensitive to erythromycin, and the clinical failures occurred (Hagelskjaer *et al,* 1998).

Penicillin IV is treatment of choice to prevent severe complications. Empiric therapy must be immediately begun in patients with a compatible clinical presentation and exposure history, as laboratory confirmation was difficult and may take more days (Walker and Reyes, 2019). Gupta *et al.* (2021) reported that IV Penicillin G at a dose of 200,000 units every 4hrs or Ceftriaxone 1gm IV daily were a must. Once patient clinically improved, IV medications can be transitioned to either Penicillin G 500mg 4 times a day or Ampicillin 500mg 4 times a day or Amoxicillin 500mg 3 times a day for 2 weeks. In penicillin allergic patients, Doxycycline 10 mg twice a day either IV or orally may be substituted.

Adults: I.V. penicillin (200,000 units every 4 hours) for five to seven days, followed if clinically improved by oral penicillin or ampicillin (500mg 4 times a day) for 7 days. Patients allergic to penicillin the alternative treatment will be tetracycline (500mg orally 4 times a day) or doxycycline (100mg orally or IV twice daily).

Children: I.V. penicillin (20,000 to 50,000 units/kg/day divided in 6 doses) to a maximum of 1.2 million units per day. Children who don't require hospitalization can be treated with oral penicillin V (25mg/kg/day in 3 or 4 divided doses). Treatment duration of was 7 to 10 days. In those with penicillin allergy with a risk consideration, alternative is doxycycline, but tetracycline can cause dental staining when administered to children, the risk of dental staining with doxycycline is minimal if a short course is given. Children more than 45 kg must receive adult dose; smaller children must receive 2 to 4mg/kg in 2 divided doses. Streptomycin is an alternative drug for adults and children with RBF. But, several limitations make its use impractical for the treatment of RBF as: drug-related toxicity, need for parenteral administration, and many pharmacies do not stock streptomycin, made it difficult to have promptly.

Prevention: Clinical course of RBF can be rapid and fatal. Thus, prevention of severe disease depends upon the increasing awareness of appropriate risk-reduction activities and possible symptoms of RBF among persons who have exposure to rats. A three-day course of oral penicillin (2g/day in adults; 25,000 to 50,000units/kg/ day in children) was reasonable after a rat bite, but antimicrobial prophylaxis efficacy is unknown.

Measures to limit RBF incidence include eradication of rodents, avoiding unpasteurized milk and potentially contaminated food & water, and hand-washing and using gloves and mask by laboratory workers dealing with rodents or cleaning rat cages. Animal handlers, laboratory workers, sanitation, and sewer workers must take precautions against exposure. Wild rodents, dead or alive, must not be touched (Cunningham *et al,* 1998).

Gupta *et al.* (2022) reported that it was a rare disease caused by two kinds of bacteria found as normal oral flora in rodents and Most cases occur in Japan, but was seen in the United States, Europe, Australia, and Africa They added that if a rodent bites a person, the area should thoroughly wash and cleansed quickly to reduce the risk of infection as untreated cases caused mortality rate up to 10%, and infection was usually treated with Penicillin or Tetracycline.

Prognosis: Without treatment, symptoms disappear within 3-4 days but regular relapses occurred 3-10 days later. An initial lesion becomes necrotic and desquamates. Relapses can stay on for a year but, normally the symptoms disappear within 2 months. But, if left untreated, RBF may be fatal due to complications (Sato *et al,* 2016).

The Egyptian rodents: More than one hundred authors Egyptian and non-Egyptian dealt with Order Rodentia that makes up the largest mammals order all-over the Arab Co-

untries with >40% of mammalian species. Osborn and Helmy (1980) gave an illustrated book on this order and other related four orders. Morsy *et al.* (1988) in north Si-nai gave an illustrated map of wild rodents. El Kady *et al.* (1989) and Shoukry *et al* (1993) in south Sinai studied seasonal variations of rodents' fauna with their ecto, endo & blood-parasites in wild and domestic rodents. Commensal rodents, *Rattus norvegicus*, *R. r. alexandrinus, R. r. frugivorous*, *Mus musculus* and others were reported in all Governorates especially in the Nile Delta (Bakr *et al,* 1996; El Shazly *et al,* 2008), and Suez Canal Zone (Morsy *et al,* 1980; 1982; Younis *et al,* 1995). But, none of them reported RBF. Fawzy *et al*. (2020 in Egypt from a tropical rusty-spotted cat isolated zoonotic *Streptobacillus felis* a bacteria causing RBF. Khatib *et al.* (2020) in Qatar reported the first RBF in a 37 years old male with multi-organ involvement required ventilator support, and treated with intravenous penicillin G.

Recommendations

Rat-bite fever is a rarely diagnosed, systemic illness caused with either *Streptobacillus moniliformis* or *Spirillum minus*. *S. moniliformis* causes most cases in USA; *S. minus* caused RBF in Asia, and worldwide.

Human infection result by a bite or scratch from an infected or colonized rat, handling of an infected rat, or ingestion of food or water contaminated with infected rat feces, particularly in infants, children, and adults in contact with domestic rodents indoors.

Symptoms of RBF start abruptly with fever, myalgias, arthralgias, vomiting, & headache followed by a maculopapular rash on extremities. Polyarthritis occurs in about half of patients. Complications include meningitis, endocarditis, pneumonia, and multiorgan failure.

Diagnosis is by culture of blood or synovial fluid samples; blood cultures must be held for 21 days, if unavailable serologic tests.

Penicillin IV is treatment of choice. Empiric therapy must be immediately begun in patients with compatible clinical pictures, and exposure history; as the laboratory confirmation was difficult and took several days.

A 3-day course of oral penicillin (2g/day in adults; 25,000 to 50,000units/kg/day in children) was effective after a bite, but antimicrobial prophylaxis efficacy is unknown.

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