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Clinical Manifestations of *Bartonella henselae* Infection Among Children: A Single Centre Study

Kliničke manifestacije infekcije uzrokovane bakterijom *Bartonella henselae* kod djece: studija jednog centra

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Abstract

Objectives: The aim of this study was to analyze clinical manifestations, epidemiology and laboratory parameters of *B. henselae* infection among children treated at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb from January 2014 until June 2019.

Materials and methods: We retrospectively analyzed the epidemiology, clinical and laboratory characteristics among children with positive indirect immunofluorescence assay for *B. henselae* IgM and IgG or positive B. henselae polymerase chain reaction from lymph node aspirate.

Results: A total of 104 patients, 47 (45,1%) female and 57 (54,8%) male were enrolled. The median age was 9,7 (range, 1,1 to 17,3 years). A history of cat contact was present in 101 (97,1%) children. Acute infection was serologically confirmed in 87 (83,6%), in 5 (4,8%) with PCR while both methods were positive in 12 (11,5%) patients. The presentation on *B. henselae* infection were regional lymphadenopathy, disseminated disease, encephalopathy and fever of unknown origin. Suppurative inflammation was the most common complication in patients with lymphadenopathy 12/92 (13%). Full recovery was the most frequent outcome (96,1%).

Conclusion: *B. henselae* infection among children is usually a mild disease presented as regional lymphadenopathy. Serology and polymerase chain reaction are useful tests for diagnosis. Treatment duration and choice of therapy depend on clinical manifestation and developed complications.

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Sažetak

Cilj: Cilj istraživanja je prikazati epidemiološke, kliničke i laboratorijske karakteristike *B. henselae* infekcije u djece liječene u Klinici za infektivne bolesti „Dr. Fran Mihaljević" u Zagrebu, u razdoblju od siječnja 2014. do lipnja 2019. godine.

Materijali i metode: Retrospektivno smo istražili kliničke karakteristike, epidemiologiju i laboratorijske parametre u bolesnika mlađih od 18 godina kod kojih je infekcija potvrđena indirektnim imunoflorescentnim testom za IgM i IgG na B. henselae ili detekcijom *B. henselae* lančanom reakcijom polimerazom iz punktata limfnog čvora.

Rezultati: Od ukupno 104 bolesnika, 47 (45,1%) je bilo ženskog i 57 (54,8%) muškog spola. Medijan dobi iznosio je 9,7 godina (raspon, 1,1 do 17,3 godina). Kontakt s mačkom zabilježen je u 101 bolesnika (97,1%). Infekcija je potvrđena serološki u 87 (83,6%), PCR metodom u 5 (4,8%), a kombinacijom obje metode u 12 (11,5%) bolesnika. Najčešća manifestacija infekcije bila je regionalna limfadenopatija, a slijede diseminirani oblik bolesti, encefalopatija i vrućica nepoznatog porijekla. U 12/92 (13%) bolesnika s limfadenopatijom došlo je do razvoja supurativne upale koja je potvrđena citološki. U 100 (96,1%) bolesnika došlo je do izlječenja.

Zaključak: Infekcija *B. henselae* u djece najčešće je blaga bolest koja se manifestira regionalnom limfadenopatijom. Serologija i lančana reakcija polimerazom metode su izbora za dijagnozu bolesti. Duljina liječenja i izbor terapije ovise o kliničkoj manifestaciji infekcije uz vrlo visoku stopu izlječenja.

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Introduction

Cat scratch disease (CSD) caused by *Bartonella henselae (B. henselae)* is the most common zoonosis. It affects all ages, but most commonly children and adolescents. The genus *Bartonella includes* 20 different species[1], of which *Bartonella henselae, Bartonella bacilliformis,* and *Bartonella quintana* are the most important pathogens in humans. CSD is caused mostly by *B. henselae*[2], a fastidious, intracellular, Gram-negative bacilli formerly known as *Rochalimea henselae.*

Typical CSD is characterized by a low-grade fever and subacute regional lymphadenitis.[3] It is usually a self-limited infection that resolves without treatment. Apart from typical CSD, the clinical spectrum of *B. henselae* infection includes disseminated disease, neurological, cardiovascular, ocular, and musculoskeletal manifestations. *B. henselae* has also been recognized to cause fever of unknown origin (FUO).[4]

Isolation of *Bartonella* species in culture requires 2 to 6 weeks incubation to primary isolation and therefore serology and polymerase chain reaction (PCR) are most commonly used tests to diagnose *B. henselae* infection. The specificity of PCR is excellent (100% in one study)[5], however it has been lacking in sensitivity, ranging from 43% to 76%.[5, 6] Indirect immunofluorescence assay (IFA) is the most frequently used serologic method. Positive IgM antibodies suggests acute infection but frequently aren't detected due to their short half-life. Thus, a negative IgM titer does not exclude infection. If serology is performed in the early infection stage, IgM and IgG titers may be low and the second serum is needed in the late stages of the disease to confirm recent infection. IgG titres decrease with time – only 25% of patients remain seropositive after one year.[7] Disadvantages of serology also include a lack of *Bartonella* species-specific antibody response, resulting in cross-activity.[8]

Materials and methods

The present study was conducted from January 2014 until June 2019 at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb. A total of 104 children with CSD were enrolled in the study. This includes patients younger than 18 years of age admitted to a paediatric department or examined at a paediatric emergency room. The CSD was diagnosed if at least 2 of 3 following criteria were fulfilled: (1) presence of clinical symptoms characteristic for CSD, (2) detection of IgM and/or IgG antibodies against *B. henselae,* (3) detection of *Bartonella* DNA in lymph node aspirate. Serum samples were obtained at the time of the admission. All samples were tested for IgM and IgG antibodies against *B. henselae.* The serologic criteria for diagnosis CSD were either single high IgG titres (≥1:512) or low IgG titres (range, 1:64 to 1:256) in combination with positive IgM titers against B. henselae (titer ≥1:20). For patients who developed lymph node suppuration, fine-needle aspiration was performed. The lymph node aspirate was assessed histopathologically and microbiologically, as well as by molecular methods. Data regarding demographics, cat exposure, laboratory and ultrasound findings, neuroimaging, treatment, and outcome were established.

Results

Among 104 children participating in the study, 47 (45,1%) were female and 57 (54,8%) male. The median age was 9,7 (range, 1,1 to 17,3 years), 14 patients (13,4%) were younger than 5 years of age. A history of cat contact was present in 101 (97,1%) children. Among 104 children, 92 (88,2%) had regional lymphadenopathy (Figure 1, Figure 2). Lymphadenopathy was most common in children older than 5 years of age. Distribution of lymphadenopathy by age is shown in Figure 3. Lymphadenopathy characteristics are summarized in Table 1.

Figure 1. Typical cat scratch disease and left axillary lymphadenopathy in a 6-year-old boy

Slika 1. Tipična prezentacija bolesti mačjeg ogreba i lijeva aksilarna limfadenopatija kod šestogodišnjeg dječaka

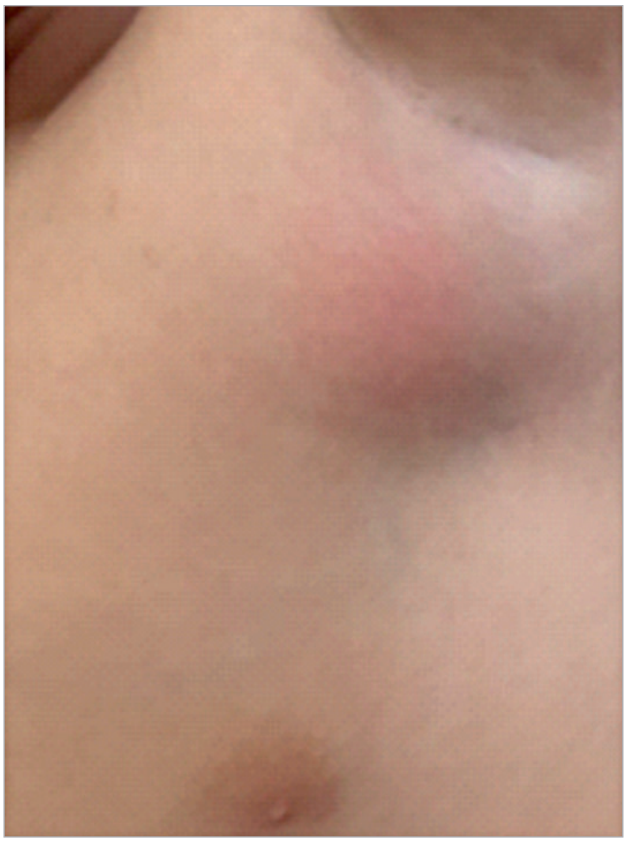


Figure 2. Cat scratch disease with supraclavicular suppurative lymphadenitis in an 8-year-old girl
Slika 2. Bolest mačjeg ogreba sa supraklavikularnim supurativnim limfadenitisom u osmogodišnje djevojčice

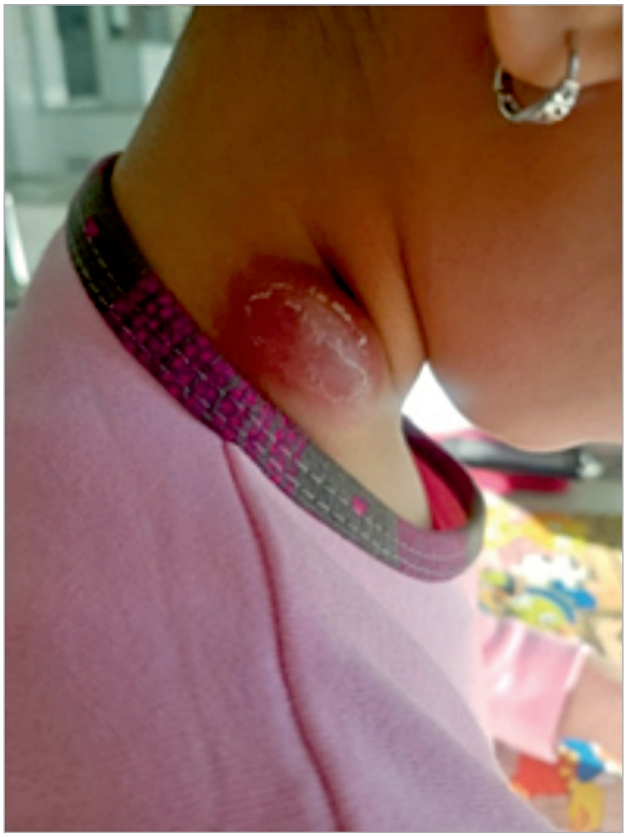


Figure 3. Distribution of cat scratch disease by age
Slika 3. Raspodjela bolesti mačjeg ogreba po dobi

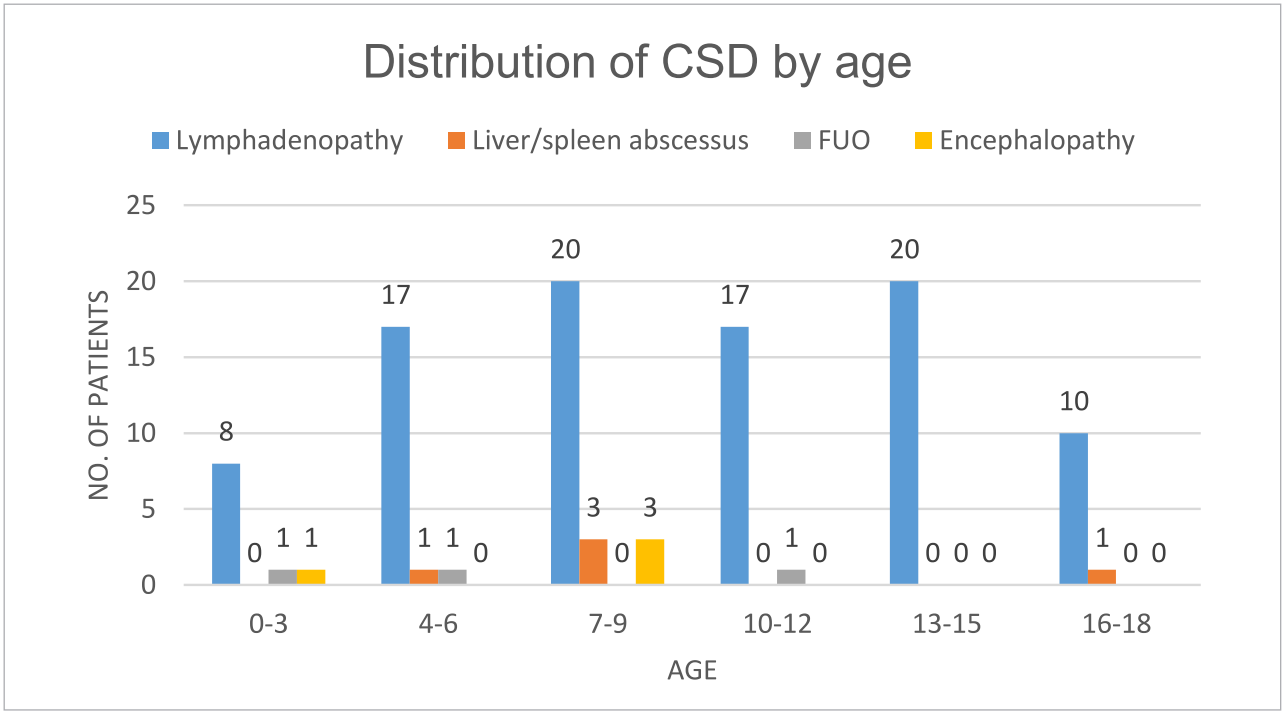


Table 1. Characteristics of 92 patients with typical lymphadenopathy caused by *B.henselae*

Tablica 1. Karakteristike 92 bolesnika s tipičnom limfadenopatijom uzrokovanom *B.henselae*

	No. (%) of patients
Fever	43/92 (46,7)
Site of lymphadenopathy	
Axillary	42 (45,6)
Cervical	37 (40,2)
Inguinal	15 (16,3)
Supraclavicular	1 (1)
Histopathological findings	
Hyperplasia	20 (42,5)
Hyperplasia with granulomatous inflammation	11 (23,5)
Suppurative inflammation	12 (25,5)
Suppurative necrosis	4 (8,5)
Diagnosis*	
serology + PCR	11 (11,9)
serology	76 (82,6)
PCR	5 (5,4)
Treatment	
Azithromycin	65 (70,6)
Azithromycin + cefazolin/cephalexin/ceftriaxone	7 (7,6)
Azithromycin + co-amoxiclav	4 (4,3)
Azithromycin + clindamycin	3 (3,2)
Azithromycin + ciprofloxacin	3 (3,2)
Azithromycin + doxycycline (+ cephalexin)	2 (2,1)
Azithromycin + rifampin	2 (2,1)
Other antibiotics (e.g., trimethoprim/sulfamethoxazole, clarithromycin, gentamycin…)	5 (5,4)
Surgical incision/drainage	10 (10,8)
No treatment	1 (1,0)

*Infection was confirmed by serology or PCR test, only in small number of patients both methods were used

In this group, azithromycin was the most commonly prescribed antibiotic (93,4%, n=86). For patients with suppurative lymphadenitis other antibiotic options included: rifampin, clindamycin, doxycycline and ciprofloxacin. Staphylococcal coinfection was microbiologically confirmed from lymph node aspirate in 5 patients. In addition to azithromycin, first-generation cephalosporins (e.g., cefazolin, cephalexin) were added in the treatment of these patients. Surgical drainage of the lymph node was performed in 10 (10,8%) patients (Table 1). Four patients with lymphadenopathy were lost in follow-up, while the others (n=88) fully recovered.

Table 2. Characteristics of 12 patients with atypical/disseminated disease caused by *B.henselae*

Tablica 2. Karakteristike 12 bolesnika s netipičnom/diseminiranom bolesti uzrokovanom *B.henselae*

Patient	Fever (days)	Lymphadenopathy	CNS	Liver abscess	Spleen abscess	Treatment
6 years, female	Yes (6)	Yes	No	No	Yes	Azithromycin, 10 days + Rifampin + gentamycin 14 days
9 years, female	Yes (14)	No	No	No	Yes	Doxycycline, 14 days
8 years, male	Yes (14)	No	No	Yes	No	Azithromycin, 5 days + TMP/SMX + rifampin, 14 days continued with gentamycin + doxycycline, 14 days
16 years, female	Yes (11)	Yes	No	Yes	Yes	Azithromycin, 5 days + Rifampin + gentamycin, 21 days continued with doxycycline, 14 days
7 years, male	Yes (26)	Yes	No	No	Yes	Rifampin + doxycycline, 21 days
3 years, male	FUO (28)	No	No	No	No	Ciprofloxacin, 14 days
11 years, female	FUO (26)	No	No	No	No	Doxycycline, 21 days
5 years, male	FUO (16)	No	No	No	No	Azithromycin, 10 days
9 years, male	No	No	Yes	No	No	Acyclovir + azithromycin, 5 days
8 years, female	Yes (5)	No	Yes	No	No	Acyclovir + azithromycin, 5 days
7 years, male	No	No	Yes	No	No	Acyclovir + azithromycin + ceftraxone 5, days
2 years, male	Yes (1)	Yes	Yes	No	No	Acyclovir + azithromycin + ceftriaxone, 5 days

Five patients presented with liver and/or spleen abscesses and three (2,8%) with FUO (Table 2). All five patients with disseminated disease had fever (range, 6 to 26 days) with average C-reactive protein values 45,1 mg/L, erythrocyte sedimentation rate and white blood cell count, 61,4 mm/hr and 12,6 x 10^9/L, respectively. According to abdominal ultrasound three patients had splenic abscesses (Figure 3), one had multiple liver abscesses and one had abscesses in liver and spleen. Liver abscesses were also detected by abdominal magnetic resonance imaging (MRI). (Figure 4) Initial therapy with azithromycin was started in three patients. Treatment was continued with different therapeutic options which included: rifampin and doxycycline or genta-

Figure 3. Abdominal ultrasound performed at admission showing multiple hypoechoic splenic lesions (abscesses) in a 7-year-old boy who presented with 3 weeks of fever and cervical lymphadenitis

Slika 3. Ultrazvuk abdomena pokazuje višestruke hipoehogene lezije slezene (apscesi) kod prijema sedmogodišnjeg dječaka s vrućicom u trajanju od tri tjedna te cervikalnim limfadenitisom

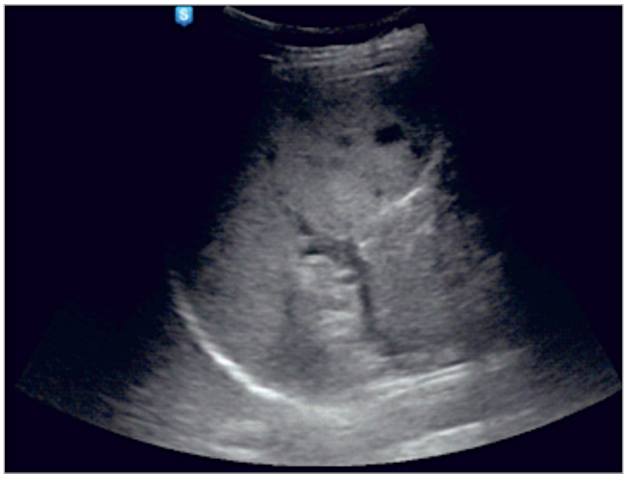
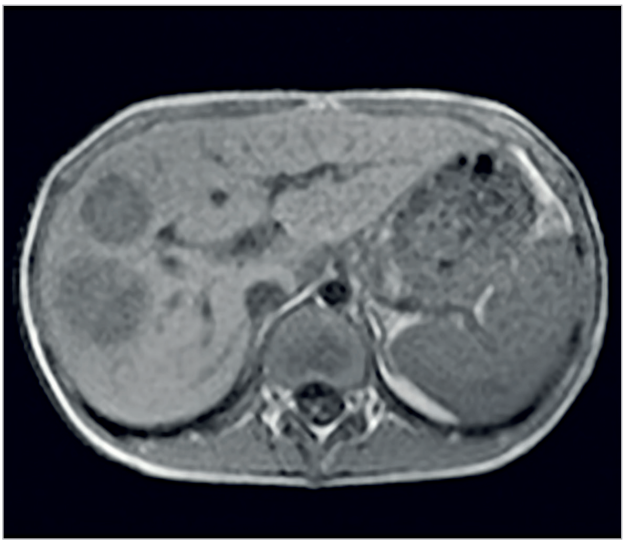


Figure 4. Abdominal MRI showing multiple liver lesions (abscesses) in an 8-year-old boy who presented with 2 weeks of fever

Slika 4. Magnetska rezonanca abdomena pokazuje višestruke lezije jetre (apscese) kod osmogodišnjeg dječaka s dvotjednom vrućicom



mycin for 21 days, rifampin and trimethoprim-sulfamethoxazole for 14 days followed by gentamycin and doxycycline for 14 days. A patient with multiple abscesses in liver and spleen was treated with a combination of rifampin and gentamycin for 21 days and continued with 14 days doxycycline therapy. Only one patient was treated with doxycycline for 14 days as a monotherapy. In all patients, the treatment led to full recovery.

Four patients presented with encephalopathy. Fever was present in two patients, and one patient had regional lymphadenopathy. Three patients had seizures at admission, one had loss of consciousness and was disoriented. In all neurologic CSD patients a brain MRI and CSF analysis was performed. One patient's brain MRI showed transverse sinus thrombosis on the left side while others had MRI without pathological findings. Lumbar puncture in two patients demonstrated discrete pleocytosis (7 cells/μl and 16 cells/μl with 36 to 59% lymphocytes, respectively) with elevated protein concentration (range, 1,0 to 1,7 g/L) and normal cerebrospinal fluid glucose concentration. CSF analysis in the other two patients was without pathological findings. In all patients, electroencephalography (EEG) showed diffuse slowing. Acyclovir and ceftriaxone were administered as an empiric therapy until the confirmation of *B. henselae* infection. Azithromycin was administered for five days. Additional therapy with low molecular weight heparin (LMWH) and warfarin for cerebral venous sinus thrombosis (CVST) was given. Recovery was complete in all patients without sequelae.

Discussion

Although recent studies suggest *B. henselae* infection is also common among adults,[9] it is still most frequently seen in children and adolescents.

The majority of patients in this study have had contact with cats but three of them didn't recall any contact with cats or kittens. Therefore, it is important to take detailed patient history prior to the diagnosis.

Clinical manifestations of *B. henselae* infection are various, extending from regional to systemic forms of the disease. Regional lymphadenopathy without fever was the most common clinical manifestation among analyzed patients. Involved lymph nodes were mostly situated at the upper extremities due to the frequency of cat scratches on the hands (axillary lymph nodes, 45,6%). Only one patient had enlarged supraclavicular lymph node. Head and neck lymphadenopathy are very common with numerous causative agents. A study by Ridder et al[10] showed that CSD is the most common infectious cause of head and neck lymphadenopathy with a frequency of 13,4%.

In the present study 80% of children with FUO had hepatosplenic manifestations of *B. henselae* infection. This fact suggests that *B. henselae* should be considered as probable cause of prolonged fever. Abdominal imaging (ultrasound, MRI, CT) is a very important step in diagnosing patients with FUO or suspected hepatosplenic involvement. Children with hepatosplenic manifestation of *B. henselae* infection had abscesses in liver or spleen and one patient in both. Liver enzymes were normal in all patients. It is interesting to note that 60% of children with the disseminated disease didn't have lymphadenopathy of any sort.

The frequency of neurological manifestations in our study was 3,8%. According to Carithers et al[11] encephalopathy is the most common neurological manifestation of *B. henselae* infection. Reported encephalopathy cases include brainstem[12] or basal ganglia involvement[13] with ischemia due to complications on blood vessels[14] or status epilepticus in children[15]. In our study, one patient developed transverse sinus thrombosis. Considering possible cerebral complications, brain MRI with contrast should be performed in all patients with neurological manifestations.

A combination of different diagnostic methods (e.g., clinical, serological, and molecular) is the basis for accurate CSD diagnosis. The initial diagnostic test for diagnosis is serology by IFA, although its specificity is low as many asymptomatic persons are seropositive due to prior animal contact. Distinguishing acute from past infection is the key for CSD treatment. Sometimes, distinction is hard because *B. henselae* IgM antibody titre is detectable for approximately three months after exposure. B. henselae IgG antibodies are detectable for approximately 22-28 weeks after exposure, while 25% of patients stay seropositive after one year.[16] In our study, serology was a useful test for diagnosing *B. henselae* infection. The detection of *B. henselae* DNA by real-time PCR has been presented as an alternative diagnostic test. Our results suggest that real-time PCR from lymph node aspirates is important for early diagnosis, with all collected samples being positive. Along with PCR lymph node biopsies from suspected CSD patients, Allizond et al[16] described high positivity values on pus drained directly from lymph nodes (35,71%) and blood (40%). In the present study, *B. henselae* was only detected by PCR from lymph node aspirate. We did not attempt to isolate *Bartonella* by PCR from blood or liver biopsies due to an early serologically diagnosed infection and the risk of possible complications caused by the biopsy.

Thus, they recommend real-time PCR on non-invasive specimens for routine use in the diagnosis of CSD in paediatric patients. Although, in comparison of these two methods being used separately (with pos-

itive PCR in 27,27% and serology in 28,28% of cases), they observed an increase in *B. henselae* positivity to up to 44,44% when combining these two methods. Poor agreement between these two methods confirms that no gold standard is established for detection of *B. henselae.*[16]

CSD is a self-limited disease that usually resolves without therapy. A study by Bass et al. showed that therapy with azithromycin led to a significant decrease (80%) in lymph node volume compared with 7% in placebo-treated patients. Aside from lymph node volume, there was no difference in clinical outcomes between study groups and there was no efficacy demonstrated for disseminated disease.[17] Since the illness is mostly uncomplicated, antimicrobial therapy is recommended for significant lymphadenopathy. First choice therapy is azithromycin and other antibiotic options include rifampin, ciprofloxacin, or trimethoprim-sulfamethoxazole. Optimal treatment for other clinical conditions caused by *Bartonella* is not yet established. There is a lack of data for the recommended treatment for immunocompromised patients and the paediatric population. According to several observational case studies, therapy of choice in the paediatric population for disseminated disease and FUO is a combination of rifampin and azithromycin. The alternative regimen is rifampin and gentamicin. The optimal therapy for neurologic and ocular disease is unknown, but antibiotic recommendation includes doxycycline and rifampin.[18]

In conclusion, *B. henselae* infection among children continues to be mild disease usually presented as regional lymphadenopathy. Although a wide spectrum of clinical symptoms is linked with *B. henselae* infection, detailed patient history and physical examination with serology and PCR are essential for establishing the diagnosis and introducing an early treatment. Given that CSD is a common cause of FUO in children, a serological test for *Bartonella* should be included in the initial evaluation of these patients.

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