

## Brucellosis in children in Bosnia and Herzegovina in the period 2000 - 2013

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### ABSTRACT

**Aim** To analyse clinical, laboratory and epidemiological characteristics of brucellosis in children in Bosnia and Herzegovina.

**Methods** The study included 246 children aged 0-18 years, who were hospitalized in Clinics and Departments for Infectious Diseases in Tuzla, Sarajevo, Banja Luka, Zenica and Bihać in the period 2000-2013, in whom the diagnosis of brucellosis was established based on anamnestic data, clinical features and positive results from blood culture and/or positive results from one of the serological tests.

**Results** In this period, a total of 2630 patients, 246 (9.35%) of whom were children, were treated from brucellosis at the Clinics and Departments in Bosnia and Herzegovina. In the majority of cases, the children were from rural parts of the country, 226 (91.87%); 214 (87.04%) cases had direct contact with sick animals, sick family member or consumption of unpasteurized dairy products from farms where brucellosis had been already established. Male children predominated, 157 (63.82%). The most frequent clinical features in affected children were fever, 194 (78.86%) and joint pain, 158 (64.22%). The average duration of antimicrobial treatment was  $42.85 \pm 10.67$  days. A total of 228 (92.68%) children were completely cured, while relapses occurred in 18 (7.32%) children.

**Conclusion** Since brucellosis is an endemic disease in Bosnia and Herzegovina, it is important that physicians in their daily practice consider brucellosis and establish proper diagnosis and therapy in children with prolonged fever, arthralgia, leukopenia and positive epidemiological data, especially in rural parts of the country.

**Key words:** clinical features, epidemiological characteristics, diagnosis, treatment

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## INTRODUCTION

Brucellosis, also known as “undulant fever”, “Mediterranean fever” or “Malta fever” is a zoonosis, and the infection is almost invariably transmitted by direct or indirect contact with infected animals or their products (1,2). The major reservoirs of the disease include goats and sheep (*Brucella melitensis*), swine (*Brucella suis*), cattle (*Brucella abortus*) and dogs (*Brucella canis*) (3,4). It is an important infection of humans in many parts of the world such as Latin America, Southern Europe, Africa and Asia. In endemic, rural parts of the country the infection frequently affects all family members, including children regardless of their gender (5-8). The disease usually starts after consumption of unpasteurized milk and dairy products, and through contact with infected animals (9). Earlier, brucellosis in children was regarded a mild and rare disease, but today it is well known that brucellosis affects all age groups, especially in endemic countries (10-12). Brucellosis in endemic regions appears on average in 3% to 10% of children (4). Acute form of brucellosis is very frequent in children, with many nonspecific symptoms, and also clinical forms which affect musculoskeletal, gastrointestinal, genitourinary, hematopoietic, cardiovascular, respiratory and central nervous systems (11,12). Clinical manifestations in children are not significantly different from manifestations in adults (2,13,14). Bosnia and Herzegovina (B&H) was free from brucellosis from 1980 until 2000. Since then, the number of infected people in the country has rapidly increased, and infections have been recorded in almost the entire territory. Brucellosis reached its peak in 2008 for the observed period 2000-2013, with 778 patients recorded (15). Published papers from different centers in B&H indicated that brucellosis has become a public health problem in the country (16-18). The aim of this study was to analyze the clinical, laboratory and epidemiological characteristics of brucellosis in patients younger than 18 years, who were hospitalized in Clinics and Departments for Infectious Diseases in B&H, in the period from 2000 to 2013.

## PATIENTS AND METHODS

The study included 246 children aged 0-18 years, in whom the diagnosis of brucellosis was established according to anamnestic data, epidemi-

ological data, clinical features and in correlation with positive results of blood cultures and/or with one of the relevant serological tests. Patients were hospitalized in six Clinics and Departments for Infectious Diseases in B&H, Tuzla, Sarajevo, Mostar, Banja Luka, Zenica and Bihać in the period 2000-2013.

A retrospective analysis was conducted of the clinical, laboratory and epidemiological data on brucellosis, collected from medical records of patients younger than 18 years of age who were treated in Clinics and Departments for Infectious Diseases in B&H. Analyzed anamnestic data included: age, gender, place of living (urban or rural region), month of disease onset, contact with animals, consumption of raw milk or cheese, family history of brucellosis, animal farming on small rural households. Clinical symptoms and signs, laboratory findings, course and outcome of the disease were particularly analyzed. The diagnosis of brucellosis was established on the basis of anamnestic and epidemiological data, clinical features, and positive results from blood culture and/or one of the relevant serological tests (Rose-Bengal, CFT, *Wright agglutination* test, ELISA test).

The study had been approved by the Research Ethics Committee of the University Clinical Centre Tuzla.

## RESULTS

In the period 2000-2013, a total of 2630 patients with brucellosis, of whom 246 (9.35%) were children, were treated in six selected Infectious Disease Clinics and Departments in B&H (Table 1). In this period there were no declared outbreaks of brucellosis, because brucellosis is endemic in B&H and the frequency of cases is counted cumulatively, year by year.

The largest number of infected children, 87 (out of 246, 35.36%) was registered in 2008, and the

**Table 1. Children with brucellosis in B&H in the period 2000-2013**

City	No (%) of patients with brucellosis	
	Total	Children (0-18 years)
Tuzla	196 (7.45)	12 (6.12)
Zenica	885 (33.65)	104 (11.75)
Sarajevo	672 (25.55)	58 (8.63)
Bihać	589 (22.40)	54 (9.17)
Mostar	64 (2.43)	8 (12.50)
Banja Luka	224 (8.52)	10 (4.46)
<b>Total</b>	<b>2630</b>	<b>246 (9.35)</b>

most cases were from Tuzla Canton, Una-Sana Canton and Central Bosnia Canton of B&H. The number of affected male children was 157 (63.82%), and female children 89 (36.18%). The average age of children was 10.76 years ± 5.19. The youngest child was a one-month old baby, and the oldest was 18 years old (Table 2).

**Table 2. Distribution of 246 children with brucellosis in B&H in the period 2000-2013 according to age groups**

Age groups	No (%) of patients
0-2	22 (8.94)
3-6	38 (15.45)
7-10	42 (17.07)
11-14	71 (28.86)
15-18	73 (29.68)
Total	246 (100)

The majority of affected children came from rural regions, 226 (91.87%), of whom 214 (87.04%) had positive epidemiological data and/or confirmed direct contact with an infected animal, an infected family member or consumption of unpasteurized milk and dairy products from households in which brucellosis was already established. The consumption of raw milk or cheese was recorded in 26 (48.14%) patients. The most frequent clinical manifestations in affected children included fever in 194 (78.86%), joint pain in 158 (64.22%), malaise and tiredness in 125 (50.81%) and night sweating in 109 (44.30%) patients (Table 3).

**Table 3. Anamnestic data in 246 children (0-18 years) with brucellosis**

Anamnestic data	No (%) of patients
Contact with animal	197 (80.08)
Sheep, goat or cow farming on a small rural household	116 (47.15)
Shepherd	52 (21.13)
Veterinarian	0 (00.00)
Veterinarian technician	0 (00.00)
Consumption of raw milk or cheese	155 (63.00)
Unknown	33 (13.41)
Family history of brucellosis	142 (57.72)

Other clinical symptoms and signs in infected children are shown in Table 4.

Elevated erythrocyte sedimentation rate (ESR) was recorded in 140 (56.81%) patients, increased values of CRP in 133 (54.06%), leucocytosis in twelve (04.87%), increased aspartate aminotransferase (AST) levels in 114 (46.34%), and increased alanine aminotransferase (ALT) levels in 40 (16.26%) patients. Decreased values of erythrocytes were registered in 58 (23.57%), thrombocytopenia in

**Table 4. Symptoms and signs in 246 children (0-18 years) with brucellosis**

Symptoms and signs	No (%) of patients
Fever	194 (78.86)
Night sweating	109 (44.30)
Headache	54 (21.95)
Weakness	125 (50.81)
Anorexia	56 (22.76)
Weight loss	43 (17.48)
Rash	11 (4.47)
Cough	41 (16.66)
Vomiting	27 (10.97)
Diarrhea	18 (7.31)
Stomach pain	42 (17.07)
Frequent urination	6 (2.44)
Dysuria	7 (2.84)
Arthralgia	158 (64.22)
One or more swollen joints	39 (15.85)
Myalgia	55 (22.35)
Hepatomegaly	27 (10.97)
Splenomegaly	15 (6.09)
Hepatosplenomegaly	58 (23.57)
Testicular swelling	5 (2.03)
Scrotal redness	5 (2.03)
Scrotal pain	6 (2.44)
Lymphadenitis	21 (8.53)

28 (11.38%) and decreased values of haemoglobin in 216 (87.80%) patients (Table 5).

The diagnosis of brucellosis was established on the basis of positive blood cultures, Rose Bengal agglutination test, Elisa test and complement fixation test (CFT) (Table 5).

**Table 5. Laboratory findings in 246 pediatric patients (0-18 years) with brucellosis**

Laboratory finding	Reference ranges	No (%) of patients
Erythrocyte sedimentation rate	≤20 mm/hours	140 (56.91)
C-reactive protein	0.0-3.3 mg/L	133 (54.06)
Leukocytes	3.4-9.7 x10 <sup>9</sup> /L	12 (4.87)
Neutrophils	44.0-72.0%	5 (2.03)
Lymphocytes	20.0-46.0%	151 (61.38)
Monocytes	2.0-12.0%	9 (3.65)
Erythrocytes	4.34-5.72%	58 (23.57)
Hemoglobin	138-175 g/L	216 (87.80)
Thrombocytes	158-424x10 <sup>9</sup> /L	28 (11.38)
Aspartate aminotransferase	15-37 U/L	114 (46.34)
Alanine aminotransferase	30-65 U/L	40 (16.26)

The number of patients with positive blood culture was 63 (25.61%). *Brucella mellitensis* was isolated from blood cultures in 20 (8.13%), *Brucella abortus* in 2 (0.81%), and *Brucella* species in 41 (16.66%) patients. The diagnosis of brucellosis was established only on the basis of serological tests in 183 (74.39%) patients. The number of patients with positive Rose Bengal (RB) test was 85 (34.55%), with positive ELISA test 35 (14.22%), and with positive RB and ELISA test

119 (48.37%), while 7 patients had positive CFT and BAB reaction (rapid agglutination for brucella).

Complications occurred in 64 (26.01%) patients as follows: monoarthritis in 15 (6.09%), polyarthritis in 16 (6.50%), synovitis in 8 (3.25%), spondylitis in 2 (0.81%), sacroileitis in 8 (3.25%), spondylodiscitis in 3 (1.22%), endocarditis in 1 (0.40%), pneumonia in 9 (3.66%), orchiepididymitis in 5 (2.03%) and splenic abscess in 5 (2.03%) patients.

All hospitalized children received symptomatic antimicrobial therapy according to standard protocols. The average duration of treatment with antibiotics was  $42.85 \pm 10.67$  days. The average hospital stay of infected children was  $26.66 \pm 10.63$  days. Tetracycline in combination with rifampicin was used in 85 (34.56%), aminoglycosides in combination with tetracycline in 70 (28.46%), gentamycin + rifampicin in 7 (2.48%), gentamycin + trimetoprim-sulfamethoxazol (TMP-SMX) in 61 (24.79%) and triple therapy: gentamycin + rifampicin + TMP-SMX in 14 (5.69%) patients. Tetracyclines were used according to standard protocol in children older than 8 years of age. No fatal cases were registered or chronic forms of the disease. Relapses were registered in 18 (7.32%) cases.

## DISCUSSION

Brucellosis was first diagnosed in B&H in 2000, and thereafter the number of patients constantly increased until 2008 (15), but from 2009, the number of patients has been decreasing. Until now the clinical, epidemiological and laboratory characteristics of brucellosis in children in B&H have not been systematically analyzed. Brucellosis in children was registered in 9.35% of the total number of cases of brucellosis in B&H in the observed period, which is very similar to the reported data on brucellosis in children in endemic regions like Mediterranean, Middle East and Latin America, where the incidence of brucella cases ranges from 3% to 10% (4). Bosilkovski et al (2010) reported that in the Republic of Macedonia in the period from 1998 to 2007, out of 550 registered cases of brucellosis, 86 (16%) were patients aged 0-14 years (19).

Human brucellosis, as shown in our study, affected people living in rural regions, and was asso-

ciated with the consumption of unpasteurized milk and dairy products. Similar data have also been reported by the majority of authors coming from other international endemic regions (9,14,20). Iranian authors have reported more frequent incidence of brucellosis in children coming from urban population (21). Shen from the USA (2014) has reported that controlling the disease in animals and humans significantly reduces the incidence of brucellosis in children in non-endemic countries (22). The fact that the majority of affected children (35.26%) were registered in 2008 is similar to reports from other endemic areas for brucellosis (19,23). Numerous studies have registered more frequent presence of brucellosis in boys than in girls (12,14,20). Data from our analysis that 58.54% of affected children were older than 10 years is also found in other reports from around the world (14,20,24).

Brucellosis is a systemic disease that can involve any organ or organ system in the human body. The majority of our patients had clinical symptoms which were described by other authors as well (2,7,25). In our patients, the disease affected mostly bones and joints in the form of monoarthritis and polyarthritis, which has also been described by authors from Iran, Greece and B&H (6,21,26). Clinical manifestations in children were not significantly different from those in adults (1,4,27).

In majority of published papers, the diagnosis of brucellosis was usually confirmed by positive blood cultures (24,25,28). Positive blood culture was recorded in 25.61% of our patients, which corresponds to data from around the world, where the percentage of positive blood culture ranges from 15% to 70% (5). *Brucella melitensis* was the most frequently isolated pathogen from blood in our country and in some other parts of the world as well (4,25). In all patients the disease was confirmed by positive blood cultures and/or serological Rose Bengal agglutination test, Elisa test, CFT.

The clinical picture of brucellosis varies from very mild to severe. Antimicrobial treatment of six weeks or longer proved successful in 92.5 % of infected children (29). According to the World Health Organization (WHO) recommendations, the choice of antimicrobials for the treatment of brucellosis in children older than 8 years of age is the same as in adults. Since tetracyclines are

contraindicated in pregnant women and children younger than 8 years of age, alternative medicines are recommended in these groups of patients (4,30). In our study, all children were cured, and relapse occurred in 7.32% of cases. The most commonly used combination of antibiotics in children older than 8 years of age was doxycycline + rifampicin in 34.56% patients. To date many clinical studies have been published about the use of various antibiotics in the treatment of brucellosis in children (6,24,27). Impressive results were obtained from a prospective study of 1100 children with brucellosis, where the treatment scheme included a 3-week combination of TMP-SMX + streptomycin, gentamicin, or rifampicin (31). In another study in which a triple therapy was administered, relapses were not registered (24). In our study, a triple therapy was administered in a total of 23 (9.35 %) patients, and no relapses were recorded either in these patients.

Our study suggests that in our country, which is

considered endemic for brucellosis, it is necessary to harmonize the views and approach to the treatment of brucellosis patients as recommended by the WHO (4).

In conclusion, brucellosis in children in Bosnia and Herzegovina is a disease that cannot be ignored. Considering its endemic nature, it is important that physicians in their daily practice consider brucellosis, and establish proper diagnosis and therapy in children with prolonged fever, arthralgia, leukopenia and positive epidemiological data, especially in rural parts of the country. Public health education is one of the most important methods for brucellosis prevention.

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#### TRANSPARENCY DECLARATIONS

Conflict of interest: none to declare.

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## Bruceloza kod djece u Bosni i Hercegovini u periodu od 2000. do 2013. godine

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### SAŽETAK

**Cilj** Ispitati kliničke, laboratorijske i epidemiološke karakteristike kod djece oboljele od bruceloze u Bosni i Hercegovini.

**Metode** U ispitivanje je bilo uključeno 246 djece, u dobi do 18 godina, koja su bila hospitalizirana u klinikama i odjelima za infektivne bolesti u Tuzli, Sarajevu, Banja Luci, Zenici i Bihaću, u periodu od 2000. do 2013. godine, a kod kojih je bruceloza dijagnosticirana na osnovu anamnestičkih podataka, kliničke slike i pozitivnih rezultata hemokulture i/ili pozitivnih rezultata jednog od seroloških testova.

**Rezultati** Od ukupno 2630 pacijenata liječenih od bruceloze u klinikama i odjelima u Bosni i Hercegovini, 246 (9,35%) su bila djeca. U većini slučajeva djeca su bila iz ruralnih područja, 226 (91,87%), a u 214 (87,04%) slučajeva imala su pozitivnu epidemiološku anamnezu o direktnom kontaktu s bolesnom životinjom, bolesnim članom porodice ili konzumacijom nepasteriziranih mliječnih proizvoda s farmi gdje je bruceloza već registrirana. Muška djeca su bila u većini, 157 (63,82%) slučajeva. Najčešći klinički simptom kod oboljele djece bila je povišena temperatura, 226 (78,86%), te bolovi u zglobovima, 158 (64,22%). Prosječno trajanje antimikrobne terapije bilo je 42,85 ± 10,67 dana. Ukupno 228 (92,68%) pacijenata bilo je potpuno izliječeno, dok se relaps pojavio kod 18 (7,32%) djece.

**Zaključak** S obzirom da je bruceloza endemska bolest u Bosni i Hercegovini važno je da liječnici u svom svakodnevnom radu imaju na umu ovu bolest i postave pravu dijagnozu, te odgovarajući tretman djeci sa simptomima u vidu produžene temperature, artralgijskim, leukopenijom i pozitivnom epidemiološkom dijagnozom, posebno u ruralnim dijelovima zemlje.

**Ključne riječi:** klinički simptomi, epidemiološke karakteristike, dijagnoza, tretman