# Brucellosis in Pediatric Populations: An 11-Year Cohort Study

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**ABSTRACT** **Background:** Brucellosis is an endemic infection affecting the Mediterranean Basin, Arabian Peninsula, India, Mexico, and South America. Data on brucellosis infections in children are limited.

**Objectives:** To review and characterize the clinical presentation of pediatric patients diagnosed with brucellosis in a tertiary medical center.

**Methods:** Retrospective data analysis was conducted on all pediatric patients from January 2010 to December 2020 admitted to the pediatric department with a diagnosis of brucellosis based on a positive serology test or growth of Brucella bacteria in blood culture.

**Results:** The study comprised 53 children aged 0–18 years. The mean age at presentation was 11.01 ± 4.91 years; 39 male (73.6%). Pre-infection exposure to unpasteurized milk or unvaccinated livestock was reported in 37 (69.8%). Fever was present in 64.6%, followed by arthralgia (49%), loss of appetite (42.3%), and weight loss (24.6%). Gastrointestinal symptoms were reported in 52.8% and included abdominal pain (34.6%), nausea (28.3%), vomiting (24.5%), and diarrhea (2.6%). Eight patients experienced pancytopenia (15.1%). The median length of intravenous antibiotic treatment was 7 days (range 3–14 days) and for oral antibiotic treatment 6 weeks (range 2–24 weeks). Most patients were initially treated with intravenous gentamycin (90.5%) and long-term oral antibiotics, most commonly doxycycline. Two (3.7%) required admission to the pediatric intensive care unit. No mortality was documented, and all cases of relapses were successfully treated.

**Conclusions:** Pediatric brucellosis is an acute febrile disease often associated with rheumatologic complaints. Patients 8–18 years of age also presented with headache, weight loss, and night sweats.

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**KEY WORDS:** brucellosis infection, fever of unknown origin, pediatric, rheumatologic complaints, zoonotic disease

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Brucellosis is one of the most common global zoonotic infections caused by the Brucella organism. The global annual infection rate is over 500,000, mostly in developing countries [1]. The Brucella organism is an aerobic gram-negative intracellular coccobacillus known to have twelve species. Strains pathogenic to humans include *B. melitensis*, *B. abortus*, and *B. suis*. Two further species, *B. canis* and *B. ceti*, rarely infect humans and a single case has been reported for *B. neotomae* [2]. The disease mainly affects livestock, but humans can be incidental hosts, primarily because of consumption of infected unpasteurized milk products, through direct contact with an infected animal, and/or by airborne inhalation [1-4].

Today, brucellosis is endemic in the Mediterranean Basin as well as in the Arabian Peninsula, India, Mexico, and Central and South America [5]. In Israel, brucellosis remains a significant infection despite intensive eradication programs. Human infections are mainly reported in rural areas such as the northern and southern districts of Israel and the Jerusalem region. Minorities, mainly Arabs and Druze, account for most cases in Israel. The lack of awareness of transmission methods among the minority population, as well as problems in implementing vaccination programs, may be to blame [6]. Despite limited data on brucellosis infections in children, most brucellosis infections in children were associated with high fevers and elevated liver enzymes, monoarthritis, hepatosplenomegaly, and lymphadenopathy [7,8]. The aim of this study was to review and characterize the clinical presentations of pediatric patients diagnosed with brucellosis in a tertiary medical center.

## PATIENTS AND METHODS

A retrospective cohort study was conducted at Hadassah Hebrew University Medical Center, a tertiary referral hospital in Jerusalem, Israel. Data were collected from electronic medical records from January 2010 to December 2020. All patients were children and adolescents aged 0–18 years admitted to the pediatric department with a diagnosis of brucellosis corresponding to ICD 9 codes 023.0, 023.1,023.2, 023.8, and 023.9. Eligibility was defined as laboratory evidence of acute infection: a positive

serology test or growth of Brucella bacteria in blood culture. Patients with missing data were excluded.

This study was approved by the Institutional Review Board (approval #0425-20 HMO). The data were divided into two age groups: 0 < 8 and 8–18. The data consisted of demographic data (including age, sex), clinical presentation, medical history, laboratory findings, hospitalization records including duration of hospitalization, antibiotic coverage, complications (including osteomyelitis, meningitis, endocarditis, epididymo-orchitis), and mortality.

### STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics for the sample demographics and clinical characteristics were calculated for mean, standard deviation, and range for the continuous variables, and frequency for the discrete variables. Differences between the subgroups and the clinical and demographic features were assessed using a Mann-Whitney test for the continuous variables and chi-square and Fisher's exact tests for the discrete variables. A *P*-value < 0.05 was considered significant.

## RESULTS

Over this 11-year period, 53 children aged 0–18 diagnosed with acute brucellosis met the inclusion criteria and were included, as shown in the cohort flow chart [Figure 1]. All the patients were admitted to the pediatric department at Hadassah Hebrew University Medical Center, a tertiary referral hospital in Jerusalem, Israel.

In total, 47 cases were diagnosed based on symptoms suggestive of brucellosis and a serological titer of 1:320 or more. All patients were hospitalized. Of the 53 children diagnosed with Brucella, the mean age at presentation was 11.017 ± 4.914 years, and 39 (73.6%) were male.

Pre-infection exposure to unpasteurized milk or to unvaccinated livestock was reported in most patients (69.8%). The demographic characteristics, presenting symptoms, signs, and clinical syndromes of the cohort are shown in Table 1. Fever was present in 64.6% (n=31). Arthralgia was present in 49% (n=26) followed by loss of appetite and weight loss in 42.3% (n=22) and 24.6% (n=18), respectively. Gastrointestinal symptoms were common presenting symptoms as well, with 34.6% (n=18) reporting abdominal pain, 28.3% (n=15) reporting nausea, 24.5% (n=13) reporting vomiting, and 22.6% (n=12) having diarrhea.

**Figure 1.** Flow chart of diagnosis of brucellosis infection according to clinical manifestations with a positive brucella blood culture or serology test. Children younger than 8 years and children between the ages of 8 and 18 years were divided into two groups

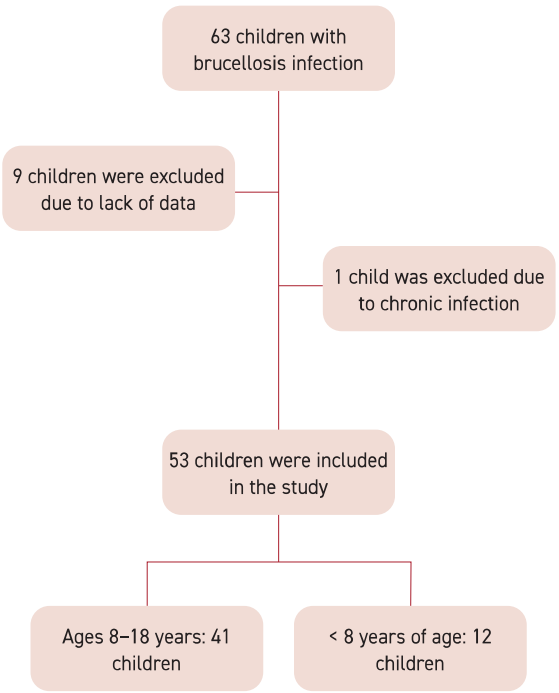



**Table 1.** Demographic characteristic, hospitalization, and mortality rates

| | Total, n=53 (100%) |
|---|---|
| **Age in years** | |
| Mean | 11.017 |
| Median | 12 |
| Standard deviation | 4.914 |
| **Sex** | |
| Male | 39 (73.6%) |
| Female | 14 (26.4%) |
| **Exposure*** | |
| Yes | 37 (69.8%) |
| No | 16 (30.2) |
| **Hospitalization duration, in days** | |
| Mean | 9.4 |
| Median | 8.0 |
| Standard deviation | 6.4 |
| **PICU admission** | |
| Yes | 2 (3.7%) |
| No | 51 (96.3%) |
| **Mortality** | |
| Yes | 0 |
| No | 53 (100%) |

*Ingestion of unpasteurized milk; direct contact with unvaccinated livestock or other infected individual

PICU = pediatric intensive care unit

All the patients had laboratory records available for review, eight patients had pancytopenia (15.1%). The median erythrocyte sedimentation rate was 20 mm/h, and the mean C-reactive protein was 1.7 mg/dl. The initial diagnosis was made by blood or bone marrow culture in 41 patients (77.3%) or by serology in 47 patients (88.6%).

The treatment regimens varied according to age group and are listed in Table 2 in addition to relapse rates and outcomes. The median length of intravenous (IV) antibiotic treatment was 7 days (range 3–14 days), and the median length of oral antibiotic treatment was 6 weeks (range 2–24 weeks). Most patients were treated initially with IV gentamycin (48;90.5%). After completion of the initial IV treatment, all patients but one were treated with long-term oral antibiotics, most commonly doxycycline, which was administered to 31 patients (58.4%), followed by combination regimens of doxycycline plus rifampicin in 10 patients (18.8%) or trimethoprim-sulphamethoxazole (TMP-SMX) in 7 patients (13.2%).

Relapse occurred in four patients (7.5%) with a recurrence of presenting symptoms and/or positive blood cultures after completion of therapy. All these patients were re-hospitalized and retreated with initial IV gentamycin for 7 days. Of these, two were also treated with doxycycline plus rifampin and two were given doxycycline alone.

Two patients (3.7%) required PICU admission. There were no cases of mortality, and all cases of relapse were successfully treated. There were no identified cases of endocarditis or meningitis. The most common complications were osteomyelitis and pancytopenia. Osteomyelitis was diagnosed in seven children (13.2%), and pancytopenia in eight (15.1%).

Fever remained the most common complaint in both age groups, n=24 (66.7%) and n=7 (58.3%), respectively; followed by arthralgia in 6 patients (54.5%) in the younger subgroup and 20 patients (50%) in the adolescent group. In most cases, pain was limited to one joint (n=46, 86.8%), most often involving the knee in 11 (21.6%) or the hip in 10; (19.6%). Gastrointestinal symptoms were more prevalent in the adolescent group. Abdominal pain was the most frequent gastrointestinal symptom, occurring in 15 adolescent patients (36.6%) followed by diarrhea, nausea, and vomiting, with incidence rates of 10 (24.4%), 10 (24.4%), and 12 (29.3%), respectively. Twelve adolescents (30%) complained of headaches compared to none in the younger group ($P < 0.035$).

The physical examination indicated lymphadenopathy in 13 adolescents (32.5%) compared to only one in the younger group (8.3%). Hepatosplenomegaly was more common in the adolescent group 29.3% ($P < 0.031$). These findings are shown in Figure 2.

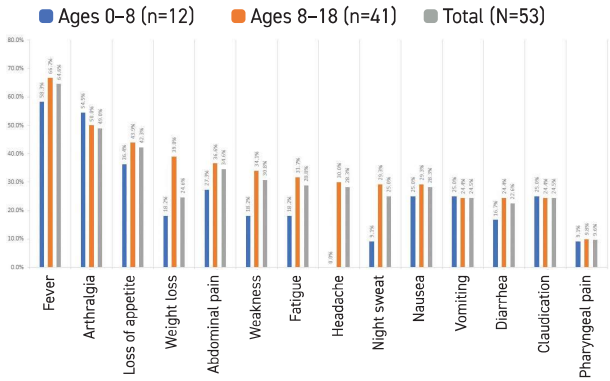
Osteomyelitis was observed in 14.6% and 8.3% ($P = 0.57$) of the adolescent and younger group, respectively. Blood culture detected the Brucella organism in 32 (80%) and 9 (81.9%) ($P = 0.89$) adolescent and child groups, respectively. Serology tests were superior to blood culture in sensitivity and detected the infection in 35 patients in the adolescent group (85%) and in all 12 children in the younger group (100%).

**Figure 2.** Clinical presentation (n=53)

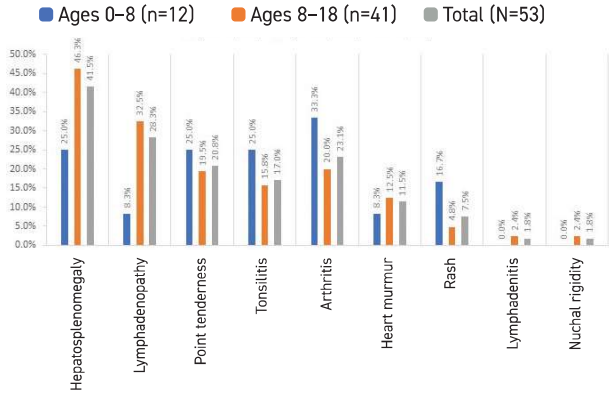
Fever ≥ 37.3°C, weight loss: decrease of ≥ 2 kg of total body weight in 2 weeks

Data were analyzes using chi-square and Fisher's exact tests

**[A]** Symptoms by age




**[B]** Diagnosis by age




## DISCUSSION

In this comprehensive review of human pediatric brucellosis, we analyzed the records of 11 years of a pediatric case series of 53 children. Due to the paucity of this infectious disease, any new results can provide a theoretical basis for clinical diagnosis, the natural history of the disease, and the outcomes of human brucellosis in pediatric populations. In this study, children were divided into two age groups, a distinction that has not been investigated previously,

**Table 2.** Diagnostic characteristics, therapeutic regimens, and outcome (n=53)

| | Ages 0 < 8 (n=12) | Ages 8–18 (n=41) | Total (n=53) | *P*-value |
|---|---|---|---|---|
| **Positive blood culture** | 81.8% (n=9) | 80% (n=32) | 77.3% (n=41) | 0.89 |
| *Brucella melitensis* | 45.5% (n=5) | 35% (n=14) | 35.8% (n=19) | 0.51 |
| Unspecified | 36.4% (n=4) | 45% (n=18) | 41.5% (n=22) | 0.6 |
| **Positive serology*** | 100 % (n=12) | 85% (35) | 88.6% (n=47) | 0.16 |
| **Treatment IV** | 91.7% (n=11) | 97.6% (n=40) | 96.2% (n=51) | 0.35 |
| Gentamycin | 83% (n=10) | 92.6% (n=38) | 90.5% (n=48) | 0.32 |
| Rifampicin | 8.3% (n=1) | – | 1.8% (n=1) | – |
| Gentamycin + rifampicin | – | 4.8% (n=2) | 3.7% (n=2) | – |
| **Treatment IV duration (days)** | | | | |
| 7 | 58% (n=7) | 69.8% (n=37) | 83% (n=44) | 0.45 |
| 14 | 25% (n=3) | 7.3% (n=3) | 11.3% (n=6) | 0.09 |
| 3 | 8.3% (n=1) | – | 1.8% (n=1) | – |
| **Treatment per oral** | 83% (n=10) | 100% (n=41) | 96.2% (n=51) | 0.008 |
| TMP-SMX + rifampicin | 58% (n=7) | – | 13.2% (n=7) | – |
| TMP-SMX | 8.3% (n=1) | 2.4% (n=2) | 5.6% (n=3) | 0.35 |
| Doxycycline | 16.6% (n=2) | 70.7% (n=29) | 58.4% (n=31) | 0.001 |
| Doxycycline + rifampicin | – | 24.3% (n=10) | 18.8% (n=10) | – |
| **Treatment per oral duration (weeks)** | | | | |
| 12 | 8.3% (n=1) | 12.1% (n=5) | 11.3% (n–6) | 0.72 |
| 6 | 83.3% (n=10) | 66% (n=35) | 84.9% (n=45) | 0.25 |
| 24 | – | 12.4% (n=1) | 1.8% (n=1) | – |
| **Hospitalization duration** | | | | |
| Mean | 11.6 | 8.8 | 10.6 | – |
| Median | 7.6 | 8.04 | 11.0 | – |
| Standard deviation | 11.02 | 4.25 | 3.2 | – |
| **Relapse** | – | 9.7% (n=4) | 7.5% (n=4) | – |
| **Complication** | 16.6% (n=2) | 34.1% (n=14) | 30.1% (n=16) | 0.25 |
| Osteomyelitis | 8.3% (n=1) | 14.6% (n=6) | 13.2% (n=7) | 0.57 |
| Pancytopenia | 8.3% (n=1) | 17.1% (n=7) | 15.1% (n=8) | 0.46 |
| Epididymo-orchitis | – | 2.4% (n=1) | 1.8% (n=1) | – |
| Endocarditis | – | – | – | – |
| Meningitis | – | – | – | – |

*Positive serology › 1:320 antibodies titer

IV = intravenous, TMP-SMX = trimethoprim-sulphamethoxazole

Blood culture, serology, treatment type, treatment duration, and relapse were analyzed using chi-square test and Fisher's exact. Hospitalization length was analyzed using Mann-Whitney test

to the best of our knowledge, and which sheds light on similarities and differences between younger children and adolescents in terms of their disease patterns. The primary transmission route of brucellosis was through the consumption of unpasteurized milk products (56%) as reported in other endemic countries [9]. Previous studies have also reported that unpasteurized dairy sales by unlicensed family-run flocks remain a significant transmission factor [10,11]. The clinical manifestations of brucellosis are widely variable, non-specific, and multi-systemic [5]. In our study, the most common clinical manifestations of human brucellosis were fever (64.6%) and arthralgia (49%). Brucellosis in the pediatric population of Israel is associated with arthralgia in 61.7% of patients and fever in 61%, like other studies [5,7,12-14]. Hepatosplenomegaly was the dominant feature of the brucellosis infection, occurring in 49.5% of the patients, as reported in other series [7,15].

A comparison of the two groups shows that adolescents were more likely to experience fever, lack of appetite, and weight loss, while arthritis, and rash. Hepatosplenomegaly occurred more fre-

quently in younger patients. Blood culture and serology tests are the standard diagnostic methods in Israel and worldwide and have a reported sensitivity of 53–90% [16] and 92–100% [17], respectively. Fruchtman and colleagues [7] found that many pediatric brucellosis patients in Israel had undetectable/low serum agglutinin levels, suggesting serology alone is not reliable. Similarly, the sensitivities in the blood cultures for the current cohort detected the Brucella organism in 80% and 81.9% of the adolescent and younger groups, respectively. Serology tests were superior to blood cultures in sensitivity, and the detection rate of infection was 85% in the adolescent group and 100% in all 12 patients in the younger group.

Osteoarticular involvement in this cohort was observed in 14.6% and 8.3% of the adolescent and younger group, respectively. This finding is similar to osteomyelitis rates reported in pediatric populations in other studies that did not differentiate by age group [12]. Endocarditis and meningitis are rare complications of Brucella infections, and studies report prevalence rates of 0.8-5% [5,12,13]. In the current cohort no cases of cardiac or nervous system involvement were documented. There was one case of epididymo-orchitis, another rare complication occurring in 2–3.8% of all cases according to large cohort studies [5,12].

Brucellosis disease can develop into a chronic disease with long-term complications. However, this is rarely true for pediatric populations [18], as demonstrated here, with only 4 children suffering from recurrent infection. There is evidence that recurrent bacteremic episodes are associated with inadequate treatment at the beginning of the infection, a low fever, low levels of IgM, and high anemia rates, which might be indicators of an impaired immune response [8].

Previous meta-analyses have reached different conclusions as to the preferred treatment regimens for brucellosis [19-22]. Generally, dual or triple regimens are advisable. In the current study, dual treatment was given to 41.5% of the patients, primarily gentamycin plus doxycycline. Triplet treatment was administered to 41.5% of the patients, composed of gentamycin, doxycycline, rifampin and rifaximin in variable combinations. The results of an Israeli study of 88 pediatric brucellosis patients showed that combined therapy with a 4-week or longer treatment period was significantly better than monotherapy or shorter treatment courses [23].

Our study has several limitations. The retrospective nature of this study prevented verification that brucellosis might have been missed if the wrong ICD code was indicated in the records. In addition, the sample was relatively small. No outpatient clinic follow-up was documented.

## CONCLUSIONS

Overall, Brucella infection is an acute febrile disease often associated with rheumatologic complaints. The older adolescent pediatric population aged 8–18 presented with additional symptoms of headache, weight loss and night sweats. Brucellosis in pediatric populations responds well to an antibiotic regime and has a low rate of complications and mortality.

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