OPEN ACCESS

GAVIN PUBLISHERS

Archives of Pediatrics

AlTeneiji M, et al. Arch Pediatr 4: JPED-166.

Research Article

DOI: 10.29011/2575-825X.100166

# Clinical Perspectives - First Insight at Pediatric Brucellosis in UAE

**Majid AlTeneiji[1], Aisha Al Khaaldi[1], Noura Lanqawi[1], Moyassar Al Tatari[2], Ghassan Ghatasheh[1], Hossam Al-Tatari[3]**

[1]Pediatric Department, Tawam Hospital, United Arab Emirates

[2]College of Medicine and Health Sciences – United Arab Emirates University, United Arab Emirates

[3]The Heart Medical Centre, United Arab Emirates

[*]**Corresponding author:** Aisha Al Khaaldi, Pediatric Department, Tawam Hospital, Khalifa Ibn Zayed Street, Al Ain, Abdu Dhabi, P.O. Box 15258, United Arab Emirates. Tel: +97137677444; Email: akhaaldi@seha.ae

**Citation:** AlTeneiji M, Al Khaaldi A, Lanqawi N, Al Tatari M, Ghatasheh G, et al. (2019) Clinical Perspectives - First Insight at Pediatric Brucellosis in UAE. Arch Pediatr 4: 166. DOI: 10.29011/2575-825X.100166

**Received Date:** 08 August, 2019; **Accepted Date:** 21 August, 2019; **Published Date:** 30 August, 2019

## Abstract

**Background:** Brucellosis in the United Arab Emirates (UAE) is estimated to be at 3.3 cases per 100,000 individuals. Presently, there is limited data on the presentation of brucellosis amongst UAE's pediatric population. Our study aims to retrospectively depict the epidemiologic, clinical course, and management of *Brucella* in our pediatric population.

**Methods:** A retrospective chart review was conducted. Data of confirmed pediatric *Brucella* cases between January 2009 and July 2017 were obtained from the health records department at Tawam Hospital. Patients aged between 0-18 years of aged were included.

**Results:** Detection rates have shown variability throughout the study, with a decline in the later years. Ninety-one patients diagnosed with Brucellosis had a mean age of 6.7 years, with a male predominance. Most patients had history of consuming unpasteurized milk, namely camel milk. Ninety-one percent had positive antibody titers which persisted after clinical resolution. The most popular regimens used were Trimethoprim-sulfamethoxazole plus Rifampicin (61%), and Doxycycline plus Rifampicin (20%).

**Conclusion:** Increased awareness, detection and thereafter management are contributing factors to the decline in Brucellosis. Agglutination testing identified majority of the patients, however it is not a sensitive marker for resolution. Different antimicrobial combinations are successful. Surveillance of medication side-effect is important to guide anti-microbial regimen changes and improve compliance.

**Keywords:** *Brucella*; Epidemiology; Microbiology; United Arab Emirates; Zoonotic Infection

## Introduction

Brucellosis is a zoonotic infection that is transmitted to humans by contact with animal secretions and/or consumption of unpasteurized animal products [1]. Brucellosis is an infection with a high rate of morbidity for humans as well as animals; and is known to be endemic in our region.

The prevalence of Brucellosis in United Arab Emirates was estimated at 3.3 cases per 100,000 individuals in 2010 [2]. Brucellosis presents a great threat to economy particularly in low-income countries [3]. The pathogenesis of the infection is highly variable and is influenced by certain factors peculiar to the host as well as those characteristic of the strain of *Brucella*; therefore, mandating the need for an extensive differential diagnosis [4]. A definitive diagnosis is made by isolating *Brucella* organisms from blood, bone marrow or other tissue. Rising titers of specific antibodies in presence of symptoms also is confirmatory of diagnosis [5]. As for the treatment regimen for this infection, fortunately, many antibiotics regimens are active against *Brucella*; however, their efficacies vary. Currently, there is no data on the presentation of brucellosis amongst UAE's pediatric population. Our study aims to retrospectively depict the epidemiologic and clinical features of brucellosis, as well as, the manifestations, complications, treatment, and prognosis in our pediatric population.

### Material and Methods

A retrospective chart review was conducted after obtaining the approval of the institutional review board (Ref: CRD 497/17 AAMD-HREC Protocol No. 531-17). Data of confirmed pediatric

*Brucella* cases between January 2009 and July 2017 were obtained from the health records department at Tawam Hospital; one of the largest tertiary hospitals in the United Arab Emirates (UAE), serving the fourth most populous city in the country. Patients aged between 0-18 years were included.

A diagnosis of *Brucella* was based on 1) Positive blood culture for *Brucella spp*. or 2) Positive *Brucella* serology of ≥1:160 using the standard Serum Agglutination Test (SAT) with positive symptoms suggestive of Brucellosis. Patients were reviewed from the time of presentation up to one year after completion of therapy. Data included patient's demographics, presenting signs and symptoms, laboratory investigations and treatment regimen. Analysis was performed with the STATA statistical package (version 15 StataCorp, college Station, TX, USA)

## Results

A total of 91 patients were diagnosed with Brucellosis during the 8-year period. The number of cases per year has shown variability throughout the study, with a decline in the later years. The highest number of diagnosed cases was in the year 2016 (Figure1).

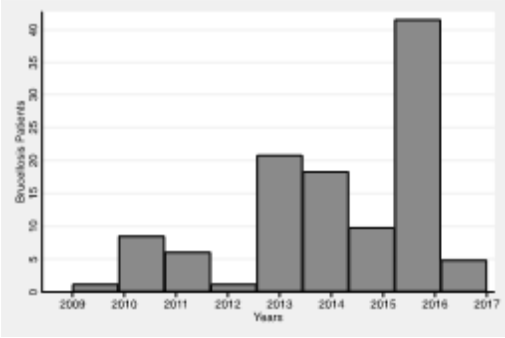


**Figure 1:** Pediatric Brucellosis cases between 2009 and 2017.

The mean age of the affected patients was 6.7 years. Males predominated the cohort, where they comprised 60% of the study population. Overall 76% of patients originated from outskirts of the city (50 Km or more from the city center). Ninety-three percent of our patients had history of unpasteurized milk consumption. Among those who had history of unpasteurized milk ingestion, 79% were from camels, 20% from goats and 1% from cows. Interestingly, 78% of the patients had a positive family history of Brucellosis.

Most reported symptoms were fever (83%), followed by joint pain (36%), abdominal pain (10%) and back pain (4%) (Table 1). Most common reported complication was osteomyelitis at 5%.

| Symptom/Sign | Number (%) | Laboratory Findings | Number (%) |
|---|---|---|---|
| Fever | 87(71%) | Anemia | 41(46%) |
| Night Sweats | 9(12%) | Leukopenia | 19 (22%) |
| Abdominal Pain | 9(10%) | Thrombocytopenia | 12(14%) |
| Joint Pain | 33(36%) | Elevated AST | 64(46%) |
| Back Pain | 3(4%) | Elevated ALT | 59(32%) |

**Table 1:** Clinical characteristics and laboratory findings of patients with pediatric Brucellosis (2009-2017).

*Brucella* diagnosis was based on positive a blood culture and/or positive antibodies to *Brucella* strains by direct agglutination testing, namely to *B.abortus* and *B.melitensis*. Sixty-five percent of our patients had positive blood cultures. Time to positivity ranged from 40 hours up to 168 hours (mean= 89hrs). As for antibody testing, 91% of our patients had positive titers to *B.abortus* and *B. melitensis*. Complete Blood Counts (CBC) were measured in 88 patients. Forty-six percent of our patients had anemia for age and gender, 22% had leukopenia and 14% thrombocytopenia. Liver enzymes were also obtained in all the patients. 30% had elevated AST and 19% had elevated ALT (Table 1).

Several antibiotic combination regimen were used in treating our patients. The following oral regimens were mostly used: Rifampicin plus Trimethoprim-sulfamethoxazole (TMP/SMX) (61%) and Rifampicin plus Doxycycline (20%). Other regimens are summarized below (Table 2).

| Treatment | Patients (%) |
|---|---|
| Rif + TMP-SMZ | 54 (61%) |
| Gent + TMP-SMZ | 3 (3%) |
| Rif + Doxy | 18 (20%) |
| Rif + Gent | 1 (1%) |
| Rif + Gent+ Doxy + TMP-SMZ | 7 (8%) |
| Rif + Doxy + TMP-SMZ | 1 (1%) |
| Rif + Gent + Doxy | 1 (1%) |
| Rif + Gent + TMP-SMZ | 4 (4%) |

**Table 2:** Antibiotic Combinations reported in managing Pediatric Brucellosis.

(Rif – Rifampin; Doxy – Doxycycline; TMP-SMZ – Trimethoprim-Sulfamethoxazole; Gent – Gentamicin)

During the course of treatment, twenty-four antibiotic regimen changes have occurred. These changes were either due to a complex medical course, inability to tolerate medication, to improve compliance or due to physician's preference. Most of the antibiotic regimen changes were due to TMP/SMX side

effects (allergy, rash, raised transaminases, thrombocytopenia or neutropenia).

Forty-nine patients had repeat of titers by the end of treatment. On follow up, 81.6% had high *B.abortus* levels, with an average repeated level of 1:237 and a maximum of 1:2600, while 67.3% had high *B.melitensis* with an average level of 1:467, and a maximum of 1:1280.

## Discussion

### Epidemiology & Burden

Alshehi, et al. estimated the prevalence of Brucellosis in the emirate of Abu Dhabi in UAE to be 3.3 per 100,000 populations in 2016 [2]. However, different numbers have been reported by various health authorities in UAE, reflecting possible under reporting and regional variations. In addition, a recently suggested transmission of *Brucella* through the hands of family and workers handling cattle may have resulted in increased recognition of cases in our region [2].

### Etiology

*Brucella* spp. are small, gram negative, non-motile, non-spore-forming, rod shaped (coccobacilli) bacterial organisms. It is a zoonotic disease caused by the ingestion of unpasteurized milk from infected animals or close contact with their secretions. Among our population the main reported species were *B.melitensis* and *B.abortus* which is endemic among animals in our region such as cows and camels. While other strains such as *B.canis* and *B.suis* are not being reported since pigs are never raised in our region and dogs are rare carriers [5] (Table 3).

| Species | Animal Host |
|---|---|
| *Brucella melitensis* | Goats, sheep, camels |
| *Brucella abortus* | Cows, other bovidae animals and camels |
| *Brucella canis* | Dogs |
| *Brucella suis* | Pigs |

**Table 3:** *Brucella* species causing human disease with their corresponding animal reservoirs.

## Clinical Presentation

Prolonged fever and arthritis are the most common presenting signs. In our cohort, almost 96% of our subjects complained of fever for 14 days or more prior to presentation. Only 32% (*n*=89) complained of joint pain; hip and knee being most affected. Unlike in adults, the sacroiliac joint and the axial skeleton were not affected among our subjects [5]. Only 5% (*n*=4) of our patients have developed osteomyelitis which is higher than reported rates of 1-2%. Other examples of rare manifestations include: meningoencephalitis, brain abscess, Guillain Barre syndrome, pneumonia, endocarditis and myocarditis, transaminitis, splenic abscess, nephritis, uveitis, thyroid abscess, immune thrombocytopenic purpura and hemophagocytic syndrome [5]**.** Individual cases of liver failure, epedidemo-orchitis, septic arthritis and hemophagocytic syndrome have occurred in our cohort.

### Diagnosis

Although blood culture is the gold standard, it's yield remains suboptimal. The explanation of the low yield of blood culture is multifactorial including patient's age [6], the prolonged or chronic clinical course, the previous exposure to antibiotics as well as technical aspects including blood sample volume, incubation time, frequency of growth monitoring, performance of blood culture media or detection systems [7-10]. In our study, all the confirmed *Brucella* cases had elevated titers. In comparison to other published reports, only 65% of the cohort had positive cultures, despite prolonged incubation [11,12]. Al-Tawfiqa JA and AbuKhamsinb A have reported positivity of blood cultures at rate of 80.7% irrespective to age. They have also concluded that patients with higher titers were more likely to have a positive culture, an association that we did not observe in our cohort [12]. In another Chinese retrospective study in 2012, all the patients diagnosed with *Brucella* had positive blood cultures [11].

ELISA IgM/IgG titers is another method of detection namely used for screening purposes. It is preferably used in the presence of clinical indicators. *Brucella* titer > 1:320 is still specific for the presence of disease even in the absence of symptoms [13]. However, the presence of high titer post successful therapy could be misleading. After completion of therapy, *Brucella* titers were repeated in half of our cohort and revealed that approximately 67-80% of patients had elevated titers despite clinical resolution; supporting the previously known fact that titers can remain high up to 2 years or more post treatment.

Other laboratory tests varied from one patient to the other in our cohort depending on their condition and clinical presentation. The most common abnormal lab findings were anemia and elevated transaminases, while the remaining parameters were marginally abnormal.

Brucellosis can cause anemia mostly due autoimmune hemolysis and may also mimic primary hematologic diseases [14]. Brucellosis might have been a direct cause for the anemia in our patients, but the lack of baseline hemoglobin level can argue against Brucellosis being a cause. On the other hand, rising transaminases could be explained by the direct involvement of the liver with resultant hepatosplenomegaly, chronic suppurative disease, and rarely hepatic granulomas [15]. The pathogenic role of brucellosis in development of liver fibrosis and cirrhosis remains limited and understudied [16].

In a pediatric Brucellosis study conducted in Texas, the authors found the WBC to range between 2900-10,600/mm$^3$. They also reported thrombocytopenia, and anemia with variable CRP and ESR levels [17]. Therefore, it seems that all of the above investigations have limited role in the initial diagnosis of Brucellosis [18].

### Management

All of our patients were treated with combination therapy. Sixty-one percent of patients received TMP/SMX and Rifampin (*n*=54). The second most popular combination used was Doxycycline and Rifampin which was used in 20% of our patients (*n*=18). Other combinations are summarized (Table 2). As for the length of therapy, almost all patients received a total 6 weeks with negligible relapse rate. There have been 24 changes of antimicrobial therapy during treatment for variety of reasons as indicated previously. There are no clear guidelines on how to optimally switch from one regimen to another. Our study is among the first to indicate the reasons of change which will help in anticipating the side effects and guide the therapy.

The literature on pediatric Brucellosis management is limited and there are only few randomized controlled trials among children. Lubani, et al. has concluded that relapse rate in combination therapy group versus monotherapy was not statistically significant, except in TMP/SMX monotherapy, were relapse rate was 30% no matter what the length of therapy was [5]. Lubani, et al. has achieved zero relapse rate after 8 weeks of treatment [5]. Since Lubani's randomized controlled trial, most of the pediatric literature focused on combination therapy for longer periods of time trying to achieve zero relapse rate [5]. At 2004, Roushan et al. found that 8 weeks of treatment with TMP/SMX plus Doxycycline is better than TMP/SMX plus Rifampin, where failure and relapse rate was 1.96 times higher in the latter [19].

One of the most recent guidelines on management of pediatric Brucellosis was published by Alshaalan MA and colleagues. They have proposed using parenteral gentamicin in combination with Doxycycline for 7 days in children aged less than 8 years followed by five more weeks of oral Doxycycline.

Those recommendations were based on several previous published papers such as Solera J. Espinosa et al. in 1997. Solera and colleagues had conducted a randomized clinical trial, which concluded that that combination of Doxycycline and Parenteral gentamicin for 7 days served as an adequate coverage, provided that the length of therapy of Doxycyclin wasn't less than 45 days.

A limitation of our study is related to the lack of needed information from the chart review, related to clinical presentation, investigations and changes in management; which is a well-known drawback expected from a retrospective study. This has encouraged us at our institution to start on formulating a local standardized Brucellosis practice guideline. Once completed a prospective cohort study of pediatric *Brucella* cases will be implemented, which will be an excellent tool to asses for the success of the newly implemented guideline, providing further information on common clinical findings and successful antibiotic regimens.

## Conclusion

Pediatric Brucellosis appears to be on an overall decline, this is particularly related to the increased public health awareness of cattle growers and measures employed by local governmental institutions. As Brucellosis can have non-specific presentation a high index of suspicion should be guided by presence of positive *Brucella* family history, consumption of unpasteurized products or animal contact. There appears to be a strong correlation between culture positivity and the agglutination tests, suggesting that it is as sensitive as the cultures in diagnosing Brucellosis. On the other hand, other ancillary investigations have limited role in diagnosis. The antimicrobial combination therapies were successful, and surveillance of medication side-effect are important to guide antimicrobial regimen changes; however, standardization of care must be implemented.

**Conflict of Interest Statement:** The authors declare that there is no conflict of interest regarding the publication of this paper.

**Ethical Approval:** Institutional review board (Ref: CRD 497/17 AAMD-HREC Protocol No. 531-17)

**Data Availability:** The data used to support the findings of this study are available from the corresponding author upon request.

**Acknowledgments:** Members of the Microbiology Department at Tawam Hospital.

## References

1. Herrick JA, Lederman RJ, Sullivan B, Powers JH, Palmore TN (2014) Brucella arteritis: clinical manifestations, treatment, and prognosis. Lancet Infect Dis 14: 520-526.
2. Al Shehhi N, Aziz F, Al Hosani F, Aden B, Blair I (2016) Human brucellosis in the Emirate of Abu Dhabi, United Arab Emirates, 2010-2015. BMC Infect Diseases 16: 558.
3. Ducrotoy MJ, Bertu WJ, Ocholi RA, Gusi AM, Bryssinckx W. et al. (2014) Brucellosis as an emerging threat in developing economies: lessons from Nigeria. PLoS Negl Trop Dis 8: e3008.
4. Elfaki MG, Alaidan AA, Al-Hokail AA (2015) Host response to Brucella infection: review and future perspective. J Infect Dev Ctries 9: 697-701.
5. Lubani MM, Dudin KI, Sharda DC, Ndhar DS, Araj GF, et al. (1989) A multicenter therapeutic study of 1100 children with brucellosis. Pediatr Infect Dis J 8: 75-78.
6. Apa H, Devrim I, Memur S, Günay I, Gülfidan G, et al. (2013) Factors affecting Brucella spp. blood cultures positivity in children. Vector Borne Zoonotic Dis 13: 176-180.

7. Espinosa BJ, Chacaltana J, Mulder M, Franco MP, Blazes DL, et al. (2009) Comparison of culture techniques at different stages of brucellosis. Am J Trop Med Hyg 80: 625-627.

8. Gotuzzo E, Carrillo C, Guerra J, Llosa L (1986) An evaluation of diagnostic methods for brucellosis-the value of bone marrow culture. J Infect Dis 153: 122-125.

9. Castaneda MR (1961) Laboratory diagnosis of brucellosis in man. Bull World Health Organ 24: 73-84.

10. Ozkurt Z, Erol S, Tasyaran MA, Kaya A (2002) Detection of Brucella melitensis by the BacT/Alert automated system and Brucella broth culture. Clin Microbiol Infect 8: 749-752.

11. Zhu D, Zhang Y, Zhong X, Ma X, Ning H, et al. (2015) Six cases of Brucella infection in children and review of literatures. Zhonghua Er Ke Za Zhi 53: 464-467.

12. Al-Tawfiq JA, AbuKhamsin AA (2009) 24-year study of the epidemiology of human brucellosis in a health-care system in Eastern Saudi Arabia. J Infect Public Health 2: 81-85.

13. Alshaalan MA, Alalola SA, Almuneef MA, Albanyan EA, Balkhy HH, et al. (2014) Brucellosis in children: Prevention, diagnosis and management guidelines for general pediatricians endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS). International Journal of Pediatrics and Adolescent Medicine 1: 40-46.

14. Eskazan AE, Dal MS, Kaya S, Dal T, Ayyildiz O, et al. (2014) Two cases of autoimmune hemolytic anemia secondary to brucellosis: a review of hemolytic disorders in patients with brucellosis. Inter Med 53: 1153-1158.

15. Ayse A, Fatih A (2011) Hepatic granulomas associated with brucellosis. Hepat Mon 11: 1-2.

16. Akritidis N, Tzivras M, Delladetsima I, Stefanaki S, Moutsopoulos HM, et al. (2007) The liver in brucellosis. Clin Gastroenterol Hepatol 5: 1109-1112.

17. Shen MW (2008) Diagnostic and therapeutic challenges of childhood brucellosis in a nonendemic country. Pediatrics 121: e1178-e1183.

18. Yoldas T, Tezer H, Ozkaya-Parlakay A, Sayli TR (2015) Clinical and laboratory findings of 97 pediatric brucellosis patients in central Turkey. J Microbiol Immunol Infect 48: 446-449.

19. Roushan MR, Gangi SM, Ahmadi SA (2004) Comparison of the efficacy of two months of treatment with co-trimoxazole plus doxycycline vs co-trimoxazole plus rifampin in brucellosis. Swiss Med Wkly 134: 564-568.