

# Pediatric brucellosis

## *An update review for the new millennium*

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### ABSTRACT

يظل داء البروسيلات أكثر نوع من أمراض الجرثومية الحيوانية المنشأ شيوعاً في العديد من البلدان حول العالم بالرغم من كونه معروف منذ فترة طويلة ويمكن السيطرة عليه حيث أنه لا يزال المرض يسبب ويؤثر بشكل خاص على الشباب. تهدف هذه الدراسة الاستعراضية تقديم نظرة لعلم الأوبئة وعلم أسباب الأمراض.

Brucellosis remains the most common bacterial zoonotic infection in many countries worldwide. Despite being long recognized and controllable, the disease still causes substantial morbidity, affecting especially the young population. The aim of this review is to provide insight to the epidemiology, etiology, clinical features, diagnosis, and management of childhood brucellosis.

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Brucellosis is one of the most common zoonotic bacterial infections and causes disease worldwide.<sup>1</sup> This disease is a major threat to global public health and is one of the greatest socioeconomic problems in many developing countries.<sup>2</sup> Brucellosis is caused by the bacterial genus *Brucella*. It affects people from all age groups, including the pediatric population. In the reported literature discussing brucellosis in children there are many discrepancies concerning the epidemiological

and clinical features as well as the outcome rates.<sup>3</sup> The purpose of this paper is to review and determine general trends with regards to the epidemiology, clinical features, diagnosis, and treatment of childhood brucellosis.

**Epidemiology.** Human brucellosis is amongst the most common zoonotic diseases with an average yearly global incidence over 500,000 and a prevalence of more than 10/100,000 population in some endemic countries.<sup>4</sup> Human brucellosis remains a major human health problem in many developing regions, especially in the Mediterranean basin, North and East Africa, the Middle East, the Arabian Peninsula, the Indian subcontinent and parts of South America and central Asia.<sup>5-6</sup> In contrast, brucellosis has been reduced or eliminated in many developed countries, including many Northern European countries. For example, only 22-47 annual cases were reported between 2010 and 2015 in Germany. Most of these cases were associated with travel to brucellosis-endemic countries surrounding the Mediterranean Sea (namely, Italy, Spain, Turkey).<sup>7-9</sup>

All age groups and both men and women are susceptible to human brucellosis.<sup>10-11</sup> However, about 11-56% of patients affected by brucellosis are younger than 14 years in endemic regions.<sup>12</sup> Brucellosis may be more common in children in developing countries due to lack of pasteurization of milk and exposure to animals in an agrarian society.<sup>12</sup>

*Brucella* species are encapsulated Gram-negative coccobacilli known to affect wild and domestic animals (namely, bovines, camels, sheep, and goats), causing abortion and infertility. *B. abortus*, *B. melitensis*, *B. canis* and *B. suis* represent the primary *Brucella* spp. capable of causing disease in humans. *Brucella melitensis* mainly infects sheep and goats and is the most virulent and primary causative agent for human brucellosis. Infection can be transmitted to humans through direct contact with infected animals or their secretions, consumption of raw milk and dairy products, and inhalation of aerosols.<sup>13</sup> Less common routes of transmission include breast feeding (mother to child), consumption of uncooked meat, and sexual contact.<sup>14-16</sup>

In addition, brucellosis is considered one of the most common laboratory-transmitted infectious diseases, accounting for 2% of all infections.<sup>17-18</sup> In Saudi Arabia, brucellosis is an endemic zoonotic disease. Ministry of Health reported incidence of 18/100,000 population/year in 2011. A number of reports from endemic areas exhibited a high percentage of pediatric patients (20-30% of affected patients).<sup>19</sup>

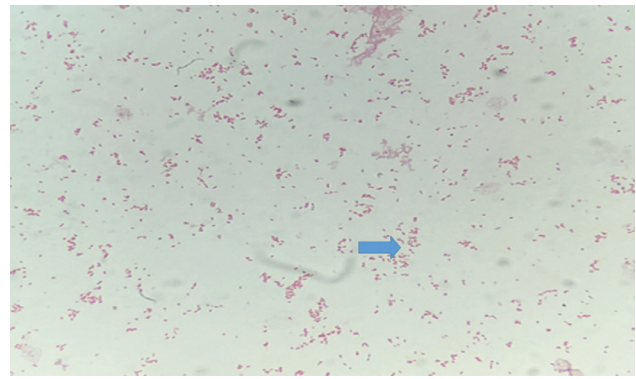
A recent study has determined that that brucellosis is a major health problem in the Kingdom of Saudi Arabia (KSA).<sup>20</sup> Although the incidence rate of brucellosis has fallen between year 2004-2012, however it was still higher than most other developed countries and developing countries. The prevalence of brucellosis among those aged <14 years was lower than other age groups. Male Saudi citizens aged 15-44 years had the highest risk of acquiring brucellosis and those aged <one year had the lowest prevalence. Al-Qassim had the greatest number of cases and was followed by Aseer in the South, Hail, and the Northern borders. The Western part had the fewest number of cases compared to other areas.<sup>20</sup>

**Etiology.** *Brucella* spp. are small Gram-negative, intracellular, nonmotile, nonsporulating, nontoxicogenic, nonfermenting, facultative coccobacilli (Figure 1). Currently, based on host preferences and phenotypic differences, *Brucella* encompasses over 10 species, *B. melitensis*, *B. abortus*, *B. suis*, *B. canis*, *B. ovis*, *B. neotomae*, *B. pinnipedialis*, *B. microti*, *B. ceti*, and *B. inopinata*.<sup>21-22</sup> *Brucella melitensis* is maintained in nature by sheep and goats, *B. abortus* by bovines, *B. suis* by swine, and *B. canis* by dogs.

Although *B. pinnipediae* and *B. cetaceae* typically affect marine animals, they are now known to be capable of causing disease in humans, mainly neurobrucellosis.<sup>21</sup>

Recently, a novel species, *B. inopinata* (strain BO1), which is associated with a breast implant infection in a patient in Oregon, was isolated from a wild rodent in Australia.<sup>22</sup>

**Clinical presentation of brucellosis in children.** Brucellosis exhibits protean clinical and laboratory characteristics that can mimic other infectious and non-infectious conditions. Patients commonly have a wide range of symptoms including undulant fever, headache, chills, myalgia, and arthralgia. The most common clinical



**Figure 1** - Gram Stained, gram negative coccobacilli (*Brucella*).

manifestations of brucellosis are fever (87.5-90%) and fatigue (70-75%) followed by sweating, myalgia, and weakness.<sup>23</sup> Brucellosis often results in systemic infections with an acute (<2 months), subacute (2-12 months), or chronic relapsing course (>one year) with severe complications.<sup>24-25</sup> Brucellosis is also associated with arthritis, spondylitis, epididymo-orchitis, acute renal failure, endocarditis, splenic abscess, abortion, and neurobrucellosis.<sup>3,26-27</sup> Childhood brucellosis produces mild to moderate disease and rarely progresses to chronicity.<sup>28</sup> Most pediatric reviews have reported a wide range frequencies of clinical manifestations in children with brucellosis. Fever and constitutional symptoms, consisting of chills, sweating, fatigue, malaise, anorexia, weight loss, abdominal pain, headaches, myalgias, and arthralgias, are amongst the most common symptoms in children.<sup>29</sup> In a Macedonian study, children comprised 317 (18.7%) of the 1,691 patients with brucellosis. The patients had a median age of 9 years, age range of 7 months to 14 years, and 201 (63.4%) patients were males. Family history of similar disease was present in 197 (62.1%) patients. The predominant clinical manifestations were fever (248, 78.2%), joint pain (228, 71.9%), and hepatomegaly (216, 68.1%).<sup>30</sup>

Arthritis was reported in 24 out of 96 (25%) child patients diagnosed with brucellosis from a children medical center in Tehran. Monoarthritis was recorded in 15 patients (62.5%) with involvement of the knee (8, 45%), hip (5, 29%), and ankle (2, 8%), while 9 (37.5%) patients suffered from polyarthritis.<sup>31</sup> In addition to osteoarticular involvement, children with brucellosis often suffer from hematologic abnormalities, such as anemia, thrombocytopenia, and pancytopenia. Disseminated intravascular coagulation and leucopenia have been reported. Brucellosis should be considered during diagnosis of patients with pancytopenia and immune thrombocytopenic purpura in endemic

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regions.<sup>32</sup> Liver involvement of hepatomegaly and splenomegaly with mild to moderate elevation in liver transaminase elevations are also common clinical symptoms of children with brucellosis. Recently, one study reported rates of 55% hepatomegaly and 60% splenomegaly within a US population.<sup>33</sup> There were many rare complications of brucellosis that have been described in children such as cardiac complications such as endocarditis and myocarditis.<sup>34</sup> Neurobrucellosis is also a rare complication which can be detected in 2–7% of child cases. The most common clinical forms of neurobrucellosis are meningitis, encephalitis, and myelitis while brain abscesses are extremely rare.<sup>35-36</sup> Brucellosis may also manifest symptoms in the eyes such as uveitis, keratitis, conjunctivitis, and neuro-ophthalmic defects. However, ocular brucellosis is rare among children.<sup>37</sup>

**Diagnosis.** Laboratory diagnosis of brucellosis relies on 3 approaches: 1) culture of *Brucella* bacteria from blood, bone marrow, tissue samples, or cerebrospinal fluid and other body fluids; 2) a compatible clinical picture, such as arthralgia, fever, sweating, chills, headache, and malaise, which is supported by the detection of specific antibodies at significant titers; 3) nucleic acid amplification detection methods. An adequate response to anti-brucellosis therapy was also accepted for diagnosis in those who were seronegative and did not yield samples with culture positive for *Brucella*.<sup>3,38-39</sup> Culturing *Brucella* is one of the most effective diagnostic methods for human brucellosis. Blood, tissue samples, pus and cerebrospinal, joint, or pleural fluid can be used to isolate *Brucella*. Automated culture systems (for example, BACTEC 9240, BacT/Alert, and Vital systems) are safe and fast methods for diagnosis and are instituted in most clinical microbiology laboratories. They enable detection of *Brucella* in more than 95% of positive cultures within a routine 1-week incubation period.<sup>40-42</sup> The current gold standard for brucellosis diagnosis depends on isolation of *Brucella* spp. from samples. However, it requires level 3 biocontainment facilities and highly skilled technical personnel to handle samples and live bacteria for eventual identification and biotyping of *Brucella* species.<sup>43</sup> Alternative brucellosis diagnostic methods include serological tests such as the Rose Bengal test, the serum agglutination test (SAT), and the antiglobulin or Coombs' test, which are based on antibody reactivity against smooth lipopolysaccharide (LPS). The veterinarian Rose Bengal slide agglutination test is used to screen sera for IgG, IgM, and IgA antibodies against *Brucella* and shows remarkable sensitivity and specificity. A reciprocal titer >160, in the

presence of a compatible clinical picture, is considered diagnostic. Because IgM antibodies tend to persist for prolonged periods, even in successfully treated patients, IgG antibodies are then titered after degrading IgM antibodies with 2-mercaptoethanol or dithiothreitol. Declining IgG titers indicate successful eradication of the organism, while persisting or increasing titers may indicate recrudescence of the disease. A newly developed Enzyme-linked immune-sorbent assay (ELISA), Brucellacapt (Vircell SL, Granada, Spain) has demonstrated improved sensitivity compared to traditional agglutination methods.<sup>40,42</sup> The most prominent laboratory abnormalities seen in acute and subacute cases were lymphomonocytosis, anemia, leukopenia, thrombocytopenia, elevated C reactive protein and ESR.<sup>44</sup> Classical biochemical methods to identify *Brucella* are time-consuming and only provide species-level information. The development of high resolution molecular methods (for instance, singleplex and multiplex PCR) have become important for *Brucella* spp. identification.<sup>45-47</sup> Moreover, rapid genus-level and species-level identification of *Brucella* is possible via 16S rRNA (ribosomal RNA) gene sequencing and real-time PCR-based high resolution melt (HRM) analysis.<sup>48-50</sup> Several genus-specific multiplex PCR systems have been developed based on primer pairs that target the IS711, IS650, 16SRNA, BCPS31, and omp2a sequences. Polymerase chain reaction can also be used for assessing treatment efficacy, species differentiation, and biotyping of isolates.<sup>43,51</sup> A study comparing the blood culture Bactec system and whole blood and serum PCR method determined that both methods (whole blood and serum PCR) were similarly sensitive and specific for diagnosing human brucellosis.<sup>52</sup> In another study, the specificity and sensitivity of SAT, Coombs Wright test, 2-mercaptoethanol test (2ME), ELISA (IgG and IgM), and PCR were compared using serum samples. Among the applied methods of diagnosis, the SAT displayed the lowest positivity rate and ELISA test had the highest efficiency. Also, the sensitivity of the PCR method was lower in comparison to ELISA.<sup>53</sup>

**Treatment.** Over the past few years, several meta-analyses of randomized controlled trials and systematic reviews on the treatment of human brucellosis (that included mostly adult patients) have been published.<sup>54-55</sup> The optimal antimicrobial treatment for brucellosis is frequently hampered by the requirement for prolonged antibiotic administration and the need to use combination therapy. Systematic review of the literature demonstrated that antibiotic treatment should be administered for 6 weeks or longer to reduce the risk



of relapse, and the authors concluded that a dual or triple antimicrobial regimen with an aminoglycoside (either streptomycin or gentamicin) for the first 2-3 weeks is preferable. The choice and duration of therapy are related to patient characteristics and the presence of a focal disease. A 3-drug regimen including aminoglycosides is advised for patients with endocarditis or meningitis.<sup>55</sup> Other regimens include a combination of doxycycline plus trimethoprim-sulfamethoxazole or a fluoroquinolone plus rifampicin. The presence of spondylitis or endocarditis usually indicates that the treatment will need to be a longer duration.<sup>56</sup> For the treatment of brucellosis in children, combination treatment regimens that include TMP-SMX, doxycycline, and rifampicin are recommended. Doxycycline is recommended only for children over 8 years old, as children younger than 8 years may be more sensitive to the side effects of doxycycline, especially tooth discoloration.

There are 2 effective treatment regimens for different age groups. For children over 8 years old, oral doxycycline (4 mg/kg/day) and rifampicin (20 mg/kg/day) are typically prescribed, and for children under 8 years old, oral trimethoprim TMP (6-8 mg/kg/day), sulphamethoxazole SMX (30-40 mg/kg/day), and rifampicin (20 mg/kg/day) are typically prescribed. Both are prescribed for 6-8 weeks. Complications and relapse can be successfully treated with triple-drug regimens. Pediatricians involved in the management of children with brucellosis should encourage compliance with the prescribed antibiotic regimen through education of patients and their families and assess treatment results through rigorous long-term follow-ups. Even when patients are adequately treated, relapses of the disease, usually milder than the initial episode, may occur at some time during the following year. Several studies reported that combined treatment of childhood brucellosis lasting at least 4 weeks results with a wide range frequency of relapses (0-32%).<sup>57-58</sup> Data on treatment of brucellosis among Saudi children is limited. A study investigating the clinical and therapeutic features of brucellosis in 163 Saudi brucellosis patients were treated successfully with antimicrobial therapy consisting of doxycycline, rifampicin, streptomycin, tetracycline and trimethoprim/sulfamethoxazole (TMP/SMX) in varying combinations. Relapse rates were 3.6% and treatment failure rates were 2.1%. Doxycycline-rifampin and doxycycline-streptomycin were the most commonly prescribed drug regimens for adults and children older than 8 years, and rifampin-sulfamethoxazole-trimethoprim for children younger

than 8 years old. All treatment failures and relapses occurred among children <10 years of age or adults >45 years old.<sup>59</sup>

Congenital brucellosis is a rare condition associated with significant morbidity and mortality. Clinical manifestations of neonatal brucellosis can vary; in areas where brucellosis is endemic, brucellosis should be suspected after excluding other microbial infections. A variety of drugs have been recommended for treatment of neonatal brucellosis. Treatment with rifampicin and trimethoprim/sulfamethoxazole for both mother and the neonate effectively relieves brucellosis without any complications. Favorable outcomes from combined use of rifampicin and trimethoprim/sulfamethoxazole for the treatment of brucellosis with has also been previously reported.<sup>60</sup>

In conclusion, in this updated review, we described the main epidemiological, clinical, and laboratory features, treatment options of brucellosis in children.

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## Statistics

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