

## BRUCELLOSIS IN SAUDI ARABIA: PAST, PRESENT AND FUTURE

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Brucellosis constitutes a major health and economic problem in many parts of the world, including countries of the Mediterranean Basin, the Middle East and the Arabian Gulf.<sup>1,2</sup> It is primarily a contagious disease of domestic animals—goats, sheep, cows, camels and dogs. Interhuman transmission of brucellosis has been rarely reported.<sup>3-5</sup> Humans are commonly infected through ingestion of raw milk, cheese or meat, or through direct contact with infected animals, products of conception or animal discharges (e.g., among shepherds, farmers and veterinarians), and through inhalation of infectious aerosols (e.g., by workers in abattoirs and microbiology laboratories).

Although sporadic human cases of brucellosis were reported between 1956 and 1982 in Saudi Arabia,<sup>6</sup> it was not until the early 1980s that the disease emerged as a major public health problem of almost epidemic proportions.<sup>7-11</sup> In the large tertiary care hospitals, the increased rates of annual admissions for brucellosis were documented in the 1980s.<sup>9-14</sup> This surge in incidence of brucellosis in animals and humans during this period has been strongly linked to the uncontrolled importation of potentially infected animals with brucellosis, widespread animal husbandry, and the prevailing habit of ingesting raw milk or its products among the population of nomadic background.

During the times of booming economic prosperity of this country in the late 1970s, the government encouraged and subsidized the establishment of many dairy farms/industries and intensive sheep/cattle breeding projects with minimal veterinary resources. This led to the uncontrolled importation of animals that were poorly screened for infection, and subsequent introduction of brucellosis into the Kingdom.<sup>15</sup> It is of interest to note that seroepidemiologic surveys for brucellosis antibodies carried out on imported and local animals sacrificed during the Hajj season of 1977 revealed higher incidences of infection among imported animals.<sup>8</sup>

The disease is caused by small, fastidious gram-negative coccobacilli of the genus *Brucella*. There are four important species pathogenic to humans: *Brucella melitensis*, found primarily in goats, sheep and camels; *Brucella abortus* in cows; *Brucella suis* in pigs; and *Brucella canis* in dogs. The *Brucella* species differ in degree of virulence and invasiveness. *B. melitensis* is the most invasive and produces the most severe disease. *B.*

*abortus* is the least invasive and causes the mildest illness. In Saudi Arabia, human infection with *B. melitensis* is commonly encountered (80%-100%), and infection with *B. abortus* is less frequent,<sup>2,7,13,16</sup> but infection with other species has not been reported. The natural reservoir of brucellosis is in domestic animals, and animal-to-animal transmission is usually venereal or by ingestion of infected tissue or milk. The infection is highly contagious in the natural animal host, and it spreads rapidly within the herd. The prevalence of human brucellosis correlates closely with the extent of animal infection in a given country. There has been a steady increase in the incidence of *Brucella* infection in the livestock in Saudi Arabia over the past two decades. In 1977, the incidence of brucellosis in goats in Makkah, Saudi Arabia was found to be 0.8%, in sheep 0.5%, in camels 2.8% and in cows 3.6%.<sup>8</sup> In 1987, the incidence of brucellosis had gone up to 18.2% in goats, 12.3% in sheep, 22.6% in camels and 15.5% in cows in the Asir region.<sup>16</sup>

Morbidity in humans in the Saudi population continues to be reported with increasing frequency from various regions of the country, particularly from the rural areas, and human infection is in the range of 1.6%-2.6%.<sup>17-19</sup> The disease presents in both sexes and in all ages. With humans, the main form of acquiring brucellosis is through ingestion of raw milk and milk products obtained mainly from infected goats or camels, a traditional custom fostered by the nomadic heritage and dietary habits of the people.

Human brucellosis is notoriously a multisystem disease with varied manifestations, and the onset may be either acute or insidious. The latter mode of presentation causes more difficulties in diagnosis. The diverse and sometimes deceptive manifestations of localized, sub-acute or chronic infection may lead to missing or delaying the diagnosis if the attending clinician has a low index of suspicion.<sup>20</sup> Morbidity depends largely upon the speed of diagnosis and the initiation of specific antimicrobial therapy. Fever with drenching sweats, lassitude, arthralgia, body aches, anorexia and weight loss are common symptoms in acute brucellosis. Fever occurs in all patients at some time during their illness, but it can wax and wane over a period of weeks to months when untreated, hence the term undulant fever.

Hepatosplenomegaly and lymphadenopathy are the usual physical findings. Occasionally symptoms related to a single organ predominate, in which case the disease is

termed localized.<sup>21,22</sup> Skeletal, gastrointestinal and hematologic complications are the most common,<sup>2,23,26</sup> but involvement of the heart and nervous system is the most serious, albeit rare.<sup>27-30</sup> Osteoarticular manifestations include peripheral arthritis, sacroiliitis, spondylitis, osteomyelitis, and bursitis.<sup>2,23</sup> Hepatitis probably occurs in most infected patients during the course of their illness, and liver function tests commonly demonstrate hepatic involvement.<sup>14,24</sup> Most patients experience nausea, vomiting, anorexia and weight loss. Rare cases of ileitis, colitis and spontaneous peritonitis have been reported.<sup>20,31</sup> Hematologic complications of mild anemia and leukopenia have been frequently associated with acute brucellosis,<sup>25</sup> but pancytopenia and thrombocytopenia are less frequently seen.<sup>26</sup>

Cardiovascular localization of *Brucella* infection can result in endocarditis, myocarditis or pericarditis.<sup>27</sup> The aortic valve has been commonly involved, followed by the mitral valve alone or both valves concurrently. Meningitis, encephalitis, meningoencephalitis, cerebellar ataxia, myelitis, radiculitis, peripheral neuritis, Guillain-Barré syndrome, and cranial nerve palsy have occurred in patients with brucellosis and involvement of the nervous system.<sup>28-30,32</sup> Psychiatric disturbances seem to be frequent, but they are not clinically recognized.<sup>20</sup> Epididymo-orchitis is the most common genitourinary complication.<sup>34</sup> A variety of pulmonary, ophthalmic and cutaneous manifestations of brucellosis have been reported.<sup>20,21,34-36</sup>

The definitive diagnosis of brucellosis is made when the organisms are isolated from blood, bone marrow, or other body fluids or tissues. A presumptive diagnosis can be made by demonstrating significant *Brucella* titers. Although most patients with brucellosis have agglutination titers of 1:160 or more, the significance of the titer level must be interpreted in light of epidemiologic evidence of a possible source of infection and clinical manifestations compatible with the disease. *Brucella* serology does not distinguish between the various species because the conventional serum agglutination test (SAT) equally detects antibodies to *B. melitensis*, *B. abortus* and *B. suis*, due to crossreactivity. Among the newer serologic tests, enzyme-linked immunosorbent assay (ELISA) appears to be the most sensitive and it may replace the SAT in the future.<sup>37</sup> Polymerase chain reaction (PCR) methods using specific primers have been developed, but further evaluation and standardization of these methods are required.<sup>38</sup>

The efficacy of antimicrobial therapy for any infection is largely judged by the rate of cure and the incidence of sequelae. Human brucellosis continues to pose a therapeutic problem despite the susceptibility of the organisms to several antibiotics; this has been attributed to the intracellular localization of the brucellae within the reticuloendothelial cells of the host, a site that is relatively inaccessible to antibiotics. The unpredictable relapses after treatment are almost invariably associated with

inappropriate choice, dosage, and length of antimicrobial therapy, or failure of patients to take prescribed drugs. Antibiotic-resistant *Brucella* strains are rarely a cause of therapy failure. Hence, the institution of a proper combination of antibiotics for a longer duration seems warranted to improve outcome and prevent relapses.<sup>39</sup> The standard therapy for acute brucellosis has been a combination of orally administered tetracycline or doxycycline for six weeks, plus streptomycin intramuscularly for the first two weeks. Treatment with orally administered rifampin, together with tetracycline or doxycycline for six weeks, is an effective alternative regimen. Treatment with cotrimoxazole is an acceptable alternative to tetracycline for use in children less than nine years of age.

Relapses occur in fewer than 10% of cases when the patient receives proper therapy early in the course of illness and rapidly responds to a repeat course of antimicrobial therapy. For localized, serious, or chronic infection, a prolonged course of 2 to 4 combined antimicrobial drugs may be required to improve outcome and prevent relapses.<sup>2,21,28</sup> Clinical trials with other antibiotics, including cephalosporins, new macrolides, and fluoroquinolones, have either given inferior results or have been too limited for proper evaluation. A safe and effective vaccine for use in humans is not yet available, but recent work on *purE* mutants of *B. melitensis* has given promising results in animals and may lead to clinical trials.<sup>40</sup>

The magnitude of human *Brucella* infection in Saudi Arabia can serve as a barometer of the prevalence of the disease in domestic animals. Eradication of brucellosis in animals is the key to prevention in humans. Attempts to eliminate brucellosis have been successful in many developed countries. These countries maintain their brucellosis-free herds by serologic testing, quarantine, and other precautionary measures at their frontiers to prevent importation of infected animals. The situation in Saudi Arabia is unique and more complicated because of continuous importation of millions of slaughter animals annually, poor animal quarantine procedures and lack of legislation to control marketing and movement of animals.<sup>15</sup> These major constraints are barriers to the achievement of control and eradication of the disease in this country. Although attempts have been made for surveillance, testing and massive immunization of animals in certain areas with high infection rates, an organized national brucellosis control program to eradicate the disease has not been undertaken. Human brucellosis acquired from milk is preventable, and legislation should be enacted to strictly require pasteurization of milk and dairy products. Nevertheless, public health education assumes an important role in preventing the transmission of brucellosis from animals to humans.

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### References

1. Matyas Z, Fujikura T. Brucellosis as a world problem. *Dev Biol Stand* 1984;56:3-20.
2. Al-Eissa YA, Kambal AM, Al-Rabeeh AA, Abdullah AM, Al-Jurayyan NA, Al-Jishi NM. Osteoarticular brucellosis in children. *Ann Rheum Dis* 1990;49:896-900.
3. Al-Eissa YA. Probable breast-milk borne brucellosis in a young infant. *Ann Trop Paediatr* 1990;10:305-7.
4. Ruben B, Band JD, Wong P, Colville J. Person-to-person transmission of *Brucella melitensis*. *Lancet* 1991;337:14-5.
5. Al-Eissa YA, Al-Mofada SM. Congenital brucellosis. *Pediatr Infect Dis J* 1992;11:667-71.
6. Arrighi HM. Brucellosis surveillance in Saudi Arabia's Eastern Province. *Ann Saudi Med* 1986;6(Suppl):5-10.
7. Kambal AM, Maghoub ES, Jamjoom GA, Chowdhury MNH. Brucellosis in Riyadh, Saudi Arabia: a microbiological and clinical study. *Trans R Soc Trop Med Hyg* 1983;77:820-4.
8. Radwan AI, Asmar JA, Frerichs WM, Bekairi SI, Al-Mukayel AA. Incidence of brucellosis in domestic livestock in Saudi Arabia. *Trop Anim Health Prod* 1983;15:139-43.
9. Norton WL. Brucellosis and rheumatic syndromes in Saudi Arabia. *Ann Rheum Dis* 1984;43:810-5.
10. Madkour MM, Mohamed AE, Talukdar MAS, Kudwah AJN. Brucellosis in Saudi Arabia. *Saudi Med J* 1985;6:324-32.
11. Al-Freih HM, Al Mohaya SA, Al Mohsen MF, et al. Brucellosis in Saudi Arabia: diverse manifestation of an important cause of pyrexial illness. *Ann Saudi Med* 1986;6:95-9.
12. Hadad Q, Smith SR. Current experience with brucellosis at Security Forces Hospital, Riyadh. *Ann Saudi Med* 1986; 6(Suppl):11-4.
13. Kiel FW, Khan MY. Analysis of 506 consecutive positive tests for brucellosis in Saudi Arabia. *J Clin Microbiol* 1987;25:1384-7.
14. Al-Eissa YA, Kambal AM, Al-Nasser MN, Al-Habib SA, Al-Fawaz IM, Al-Zamil FA. Childhood brucellosis: a study of 102 cases. *Pediatr Infect Dis J* 1990;9:74-9.
15. Hafez SM. The impact of uncontrolled animal importation and marketing on the prevalence of brucellosis in Saudi Arabia. *Ann Saudi Med* 1986;6(Suppl):15-8.
16. Bilal NE, Jamjoom GA, Bobo RA, Aly OFM, El-Nashar NM. Brucellosis in the Asir region of Saudi Arabia. *Saudi Med J* 1991;12:37-41.
17. Al-Nasser A, Al-Aska A, Al-Balla S, Al-Mofleh IA, Al-Sekait M, Hassan OS. Epidemiology of brucellosis in Saudi Arabia. *Ann Saudi Med* 1991;11:245.
18. Al-Sekait MA. Epidemiology of brucellosis in Northern Saudi Arabia. *Saudi Med J* 1992;13:296-9.
19. Al-Balla Suliman R. Epidemiology of human brucellosis in Southern Saudi Arabia. *J Trop Med Hyg* 1995;98:185-9.
20. Al-Eissa Y, Al-Zamil F, Al-Mugeiren M, Al-Rasheed S, Al-Sanie A, Al-Mazyad A. Childhood brucellosis: a deceptive infectious disease. *Scand J Infect Dis* 1991;23:129-33.
21. Al-Eissa YA. Unusual suppurative complications of brucellosis in children. *Acta Paediatr* 1993;82:987-92.
22. Akhtar M, Ali A. Pathology of brucellosis: a review of 88 biopsies. *Ann Saudi Med* 1989;9:247-53.
23. Rajapakse CAN, Al-Aska AK, Al-Orainey, Halim K, Arabi K. Spinal brucellosis. *Br J Rheumatol* 1987;26:28-31.
24. Al-Aska AK. Gastrointestinal manifestation of brucellosis in Saudi Arabian patients. *Trop Gastroenterol* 1989;10:217-9.
25. Al-Eissa Y, Al-Nasser M. Haematological manifestations of childhood brucellosis. *Infection* 1993;21:23-6.
26. Al-Eissa YA, Assuhaimi SA, Al-Fawaz IM, Higgy KE, Al-Nasser MN, Al-Mobaireek KF. Pancytopenia in children with brucellosis: clinical manifestations and bone marrow findings. *Acta Haematol* 1993;89:132-6.
27. Al-Kasab S, Al-Fagih MR, Al-Yousef S, et al. Brucella infective endocarditis: successful combined medical and surgical therapy. *J Thorac Cardiovasc Surg* 1988;95:862-7.
28. Bashir R, Al-Kawi MZ, Harder EJ, Jinkins J. Nervous system brucellosis: diagnosis and treatment. *Neurology* 1985;35:1576-81.
29. Al-Orainey IO, Laajam MA, Al-Aska AK, Rajapakse CN. Brucella meningitis. *J Infect* 1987;14:141-5.
30. Al-Eissa YA. Clinical and therapeutic features of childhood neurobrucellosis. *Scand J Infect Dis* 1995;27:339-43.
31. Halim MA, Ayub A, Abdulkareem AM, Ellis ME, Al-Gazlan S. Brucella peritonitis. *J Infect* 1993;27:169-72.
32. Al-Eissa YA, Al-Herbish AS. Severe hypertension: an unusual presentation of Guillain-Barré syndrome in a child with brucellosis. *Eur J Pediatr* 1996;155:53-5.
33. Ibrahim AIA, Awad R, Shetty SD, Saad M, Bilal NE. Genitourinary complications of brucellosis. *Br J Urol* 1988;61:294-8.
34. Patel PJ, Al-Suhaibani H, Al-Aska AK, Kolawole TM, Al-Kassimi FA. The chest radiograph in brucellosis. *Clin Radiol* 1988;39:39-41.
35. Abdelrazak M. Brucella optic neuritis. *Arch Intern Med* 1991;151:776-8.
36. Al-Orainey IO, Siddique MA, Wright SG, Al-Hokail AAR, Rajapakse CNA. Skin lesions in brucellosis: report of two cases. *Ann Saudi Med* 1988;8:219-20.
37. Gad El-Rab MO, Kambal AM. Evaluation of a brucella enzyme immunoassay test (ELISA) in comparison with bacteriological culture and agglutination. *J Infect* 1998;36:197-201.
38. Matar GM, Khneisser IA, Abdelnoor AM. Rapid laboratory confirmation of human brucellosis by PCR analysis of a target sequence on the 31-kilodalton *Brucella* antigen DNA. *J Clin Microbiol* 1996;34:477-8.
39. Al-Eissa YA, Al-Zamil FA, Al-Nasser MN. Duration of chemotherapy for childhood brucellosis. *Pediatr Infect Dis J* 1994;13:335.
40. Crawford RM, Van de Verg L, Yuan L, et al. Deletion of pureE attenuate *Brucella melitensis* infection in mice. *Infect Immun* 1996;64:2188-92.