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Brucellosis in Immunocompromised Individuals

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Abstract: ***Brucellosis is an infectious disease of animals (zoonosis) that is transmittable to humans by wild and domestic animals. Several Brucella species have been identified, 6 of which are human pathogens. The incidence of brucellosis varies considerably from time to time and from one country to another. Recently, brucellosis has been increasingly recognized in patients with comorbid medical conditions and in immunocompromised individuals. The course of the disease varies considerably from totally asymptomatic to a severe illness that is potentially fatal. Complications, chronic infections and relapses are prone to occur particularly in patients with low immunity. Human brucellosis has protean clinical manifestations and the occasionally misleading clinical picture may contribute to under - diagnosis of the disease. Consequently, complications may evolve and treatment may be delayed. Therefore, sustaining a high index of suspicion is important as early diagnosis and prompt therapy improve the outcome and prevent complications.***

Keywords: brucellosis, immunocompromised hosts, complication, prevention

1. Introduction

Recently, brucellosis has been increasingly recognized in patients with comorbid medical conditions and in immunocompromised individuals [1]. The infective dose is relatively low as 10 to 100 organisms are sufficient to cause the disease. The duration of the incubation period ranges between one week and several months. During this period of time, the clinical features are non - specific [1]. Brucellosis may present as an acute febrile illness or as a chronic medical condition. Additionally, it can cause a localized infection or a generalized disease with systemic manifestations. The course of the disease varies considerably from totally asymptomatic to a severe illness that is potentially fatal. Complications, chronic infections and relapses are prone to occur particularly in patients with low immunity [2].

Human brucellosis has protean clinical manifestations and the occasionally misleading clinical picture may contribute to under - diagnosis of the disease. Consequently, complications may evolve and treatment may be delayed [3]. Therefore, sustaining a high index of suspicion is important as early diagnosis and prompt therapy improve the outcome and prevent complications.

2. Material and Methods

This review on *Brucella* infections in immunocompromised individuals, will be an update on the following aspects of brucellosis: (1) epidemiology, pathogenesis, microbiology, clinical manifestations and complications, (2) *Brucella* infections in various categories of immunocompromised individuals, and (3) diagnostic techniques, available therapies, prevention and control of the infection. However, particular attention will be given to brucellosis in recipients of stem cell and solid organ transplantation.

3. Results and Discussion

Incidence and epidemiology

Brucellosis is an infectious disease of animals (zoonosis) that is transmittable to humans by wild and domestic animals [4]. Several *Brucella* species have been identified, 6 of which are human pathogens [5]. The incidence of brucellosis varies considerably from time to time and from one country to another [6]. Several studies have shown that the annual incidence of brucellosis per million of population is as follows: 0.09 in Canada; 0.3 - 0.9 in the United States of America, the United Kingdom, Sweden and the Netherlands; 211 - 495 in Turkey; 606 in Mongolia; 362 - 880 in Kyrgyzstan; 214 - 1376 in Saudi Arabia; 239 - 1416 in Iran and 1603 in Syria [7]. The infection is global in distribution, but it is endemic in the Mediterranean and Middle East regions, Indian subcontinent, Mexico and parts of Central and South America [8]. In the era of globalization and international tourism, brucellosis has become a common imported disease in the developed world [9]. It is estimated that 60% of emerging human pathogens are zoonotic [16]. Brucellosis is the commonest zoonotic infection worldwide as it has been reported in 56 countries and as more than 500, 000 new cases of brucellosis are reported annually [10]. Additionally brucellosis is a notifiable disease in most countries [11]. The epidemiology of human brucellosis has changed over the last 25 years [12]. Unfortunately, in many *Brucella* - endemic countries, the health systems are weak and official data are likely to underestimate the true burden of the disease [13]. Also, local traditional medicines including herbal medications are commonly used to treat *Brucella* infections in certain countries such as Tanzania [14]. The resurgence and the recent increase in the incidence of brucellosis can be attributed to: (1) socioeconomic changes, (2) wars and political turbulence in some countries that are endemic for the disease, (3) inadequate infection control programs in some countries, (4) international tourism due to the recent ease of human travel, (5) uncontrolled animal transportation across open borders, (6) the complexity of the disease which has different cycles of expansion and regression, and (7) the recent increase in the number of immunocompromised individuals and their longer

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survival which is mainly attributed to the recent improvements in medical care [9].

Risk factors and transmission of brucellosis

The risk factors for *Brucella* infection include: consumption of raw milk and unpasteurized dairy products, direct contact with animals and their products, male sex and age between 40 and 49 years [2]. Brucellosis is an occupational disease that poses risk to shepherds, abattoir workers, veterinarians and personnel working in diary - industry and microbiology laboratories [2]. Brucellosis is commonly transmitted by: (1) consumption of unpasteurized or contaminated animal dairy products, (2) direct contact with infected animal parts and (3) inhalation of infected aerosolized particles. Less common means of transmission of the disease include: (1) person to person transmission, (2) blood transfusion, (3) transfusion of harvested bone marrow in recipients of hematopoietic stem cell transplantation (HSCT), and (4) sexual transmission, as in the few reported cases of sexually transmitted brucellosis in humans, the organisms were either cultured from semen or their presence in serum was demonstrated by polymerase chain reaction (PCR) [2].

Microbiological aspects

The organism is a Gram negative, non - spore - forming, coccobacillus [7]. It is aerobic, partially acid fast and has short rods [11]. It is localized predominantly to organs with numerous macrophages such as lungs, liver, spleen, bone marrow and synovium [7]. Several species have been recognized and the following 6 species are pathogenic to humans: *B. melitensis*, *B. abortus*, *B. suis*, *B. canis*, *B. ceti* and *B. pinnipedialis [*5]. The organism is shed in milk, fetal membrane, semen and uterine discharges. Reservoirs of *Brucella* infection include goats, sheep, camels, cattle, dogs, pigs and deers [2].

B. canis infections are rarely reported in humans. Between 1999 and 2010, only 11 cases of *B. canis* infection in humans had been reported in Japan [15]. In a febrile person who has signs and symptoms of unknown cause and history of contact with animals, *B. canis* infection should be considered and appropriate action to prevent spread of infection should be taken [15].

Brucellosis in immunocompromised patients

In immunocompromised individuals: (1) the clinical manifestations of brucellosis may be similar to those in immunocompetent individuals, (2) the diagnosis may be delayed due to overlapping between the clinical features of brucellosis and those of the underlying disease, (3) more complications are prone to develop and (4) treatment of brucellosis may be delayed and may become difficult due to the interactions between anti - *Brucella* medications and cytotoxic chemotherapeutic agents as well as immunosuppressive drugs [16].

Brucellosis in patients with hematological disorders:

Brucellosis has been reported in patients with a variety of hematological diseases such as: acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, multiple myeloma, polycythemia rubra vera and myelofibrosis [17]. In patients with malignant and pre - malignant hematological disorders living in endemic areas, brucellosis can cause: febrile illnesses; pancytopenia; systemic infections including endocarditis, meningoencephalitis, pulmonary insufficiency and splenic abscess; complicated bacteremia and serious morbidity [18] Additionally, several cases of febrile neutropenia caused by infection with *Brucella* species have been reported in patients with malignant hematological disorders living in geographic locations that are endemic for brucellosis [19]. Brucellosis may develop at presentation of the hematological malignancy or even if the disease is under control [20]. Presentation of brucellosis is usually with fever and pancytopenia, although some patients may present with clinical manifestations similar to those in immunocompetent individuals [21]. Early diagnosis of brucellosis and prompt administration of appropriate antimicrobial therapy usually improve the outcome in such immunocompromised individuals [22]. Antimicrobial drug therapy can be administered simultaneously with cytotoxic chemotherapy to control both brucellosis and hematological disorders but in case of bacteremia, prompt antimicrobial therapy may become essential [23].

Brucellosis and renal disease

Brucellosis has been reported in patients with end stage renal disease (ESRD) living in endemic areas [25]. Presentation is usually with FUO but the infection may be complicated by neurobrucellosis, paravertebral and epidural abscesses and peripheral arthritis [24]. Brucellosis has been reported to cause ESRD, pyelonephritis, interstitial nephritis, mixed cryoglobulinemia and IgA nephropathy [26]. Tissue biopsies in patients having renal involvement by brucellosis have shown: mesangial and diffuse proliferative glomerulonephritis, rapidly progressive and focal segmental glomerulonephritis as well as exudative glomerulonephritis [27]. Antimicrobial therapy given for brucellosis usually improves the renal involvement [28].

Brucellosis in patients with HIV infection

Despite the apparent poor association between HIV and brucellosis and that the impression that HIV infection does not seem to increase the incidence of brucellosis, several cases as well as case series on the development of brucellosis in HIV infected individuals have been reported [29]. The risk factors for *Brucella* infection in HIV patients are male sex and intravenous drug abuse [30]. Clinical presentation is usually with fever, sweating, arthralgia and myalgia. Focal disease and recurrence of symptoms, but not disease relapse, may occur and high *Brucella* serological titers are usually encountered [31]. Brucellosis is not an opportunistic infection in patients with HIV or acquired immunodeficiency syndrome even in endemic areas and most HIV patients co - infected with *Brucella* species have benign clinical course of their brucellosis [32].

Brucellosis coexisting with other infections

Brucellosis has been reported in patients having other infections such as leishmaniasis, tuberculosis, hepatitis C infection and viral hemorrhagic fevers. Cytopenias are major complications in these patients. The development of further complications can be prevented by simultaneous treatment of both infections and provision of supportive measures [33].

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Brucellosis coexisting with other chronic medical illnesses

Brucellosis has also been reported in patients having chronic medical illnesses such as chronic osteoarthritis, polycythemia rubra vera, liver cirrhosis, pulmonary fibrosis and rheumatoid arthritis (RA). Early institution of appropriate antimicrobial therapy is essential to control *Brucella* infection and to prevent complication [34].

Approximately 40% of patients having brucellosis develop systemic and chronic manifestations similar to those of chronic fatigue syndrome or myalgic encephalomyelitis [35]. Also, patients infected with *Brucella* species may present with neurological manifestations indistinguishable from those of with multiple sclerosis. However, old and new literatures provide conflicting data on the association between brucellosis and multiple sclerosis [36].

Hematological abnormalities in brucellosis

Hematological abnormalities in brucellosis include: leukopenia with relative lymphocytosis, neutropenia, anemia, thrombocytopenia, pancytopenia, DIC, microangiopathic hemolytic anemia (MAHA), hypersplenism, and elevation of ESR as well as CRP [37]. However, none of these hematological abnormalities is specific or characteristic for brucellosis [38].

Thrombocytopenia is occasionally encountered and may be severe. Thrombocytopenic purpura has also been reported in patients with brucellosis. Early recognition of this complication is essential as CNS hemorrhage is associated with high mortality rates. Nevertheless, treatment of brucellosis in addition to corticosteroid therapy can control both disorders [39]. Hemolytic anemia that may be acute and Coomb's positive can also be seen [40]. Despite the severity of MAHA, complete recovery has been encountered with early and prompt therapy using plasma exchange, antimicrobial therapy for brucellosis and corticosteroids [41]. Capillary leak syndrome, similar to that occurring as part of graft versus host disease following HSCT, has been reported in patients with brucellosis [204]. Patients may present with: fever, sweats, weakness, hepatosplenomegaly peripheral edema, pancytopenia, hypoalbuminemia and elevation of liver enzymes. Anti - *Brucella* therapy usually results in the resolution of the clinical and the laboratory manifestations [42].

In patients living in areas that are endemic for brucellosis, presentation with FUO and pancytopenia should alert treating physicians to the possibility of having an underlying primary hematological disorder such as myelodysplastic syndrome or myelofibrosis [43] In patients having brucellosis and hematologic malignancy, simultaneous treatment of both the infection and the hematologic malignancy should be considered [44].

Bone marrow examination in brucellosis may show the following findings: (1) normocellular, hypercellular or hypocellular marrow, (2) granuloma formation, (3) hemophagocytosis with histiocytic hyperplasia, (4) erythroid hyperplasia, and (5) infiltration by plasma cells or leukemic blasts on very rare occasions as shown in Table 3, [206]. Brucellosis causes granulomas in the bone marrow and other tissues and these granulomas are usually small, non - caseating and they resemble sarcoid granulomas [189]. Histologically, they consist of epitheloid cells, polymorphonuclear leukocytes, lymphocytes and few giant cells [45].

Brucellosis and FUO

In a study, performed in India, that included 283 patients with FUO: *Brucella* serology was found to be positive in 3.5 - 6.0% of patients having FUO. The incidence of positive *Brucella* serology varied according to the occupation of the participant and the type of serological test used [246]. In another Indian study on the etiology of FUO, 44% of patients in whom a cause of FUO was found had infectious etiology and infections were the commonest cause of FUO followed by collagen vascular diseases [46]. The most common infectious causes of FUO are: tuberculosis, endocarditis, typhoid fever, brucellosis, *CMV* infection and acquired immunodeficiency syndrome in western countries [46]. In patients with FUO, clinical features may give more clues to the diagnosis of collagen vascular disorders, while invasive procedures such as tissue biopsies, followed by cultures and cytology contribute greatly to the diagnosis of cancer and infectious diseases [47].

4. Conclusions

Brucellosis is a common global re - emerging zoonosis that represents a major health and economic burden in many countries. *Brucellae* are Gram - negative, intracellular coccobacilli that predominantly affect organs rich in macrophages. Several species have been recognized, 6 of them are human pathogens. Infection can be acquired by: consumption of unpasteurized dairy products, direct contact with animals, blood product transfusion, sexual transmission, travel in the era of globalization and laboratory exposure. The recent immunologic, genetic and genomic advances have translated into better understanding of the pathogenesis of brucellosis and are likely to be utilized well in the vaccination, prevention and therapy of this disease.

Brucellosis has recently been increasingly recognized in immunocompromised individuals such as those with hematologic malignancy, solid tumors, HSCT, SOT, ESRD and other comorbid medical conditions. Brucellosis has rather unpredictable clinical manifestations and a variable clinical course with specific complications, hence many cases remain unrecognized. Mortality rate is less than 5% of cases and most deaths are due to complicated infections. Management of brucellosis in immunocompromised hosts requires special attention to a number of factors including the specific drugs to be used and the duration of therapy.

The diagnosis of brucellosis can provisionally be made on clinical grounds but confirmation requires certain laboratory data. The gold standard diagnostic test is the isolation of the organism from blood cultures. The lysis concentration methods and the automated cultural techniques have improved the yield rates significantly. Several serological techniques are employed in diagnosing acute, chronic and relapsing brucellosis. New diagnostic techniques such as

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molecular tests, genetic and immunological markers in addition to PET scans will definitely aid in the diagnosis and follow - up of patients having brucellosis, particularly immunocompromised ones living in endemic areas.

Monotherapy may be associated with therapeutic failure and relapse, while drug combinations are usually effective. The most commonly used regimens are composed of: doxycycline combined with rifampicin and/or an aminoglycoside. The duration of treatment depends on the: duration of the illness, presence or absence of complications and primary site of infection. The new flouroquinolones, tigecycline, levamisole and IFN - γ are likely to be incorporated into future management of brucellosis. Adverse effects of anti - *Brucella* therapy, interaction with immunosuppressive agents used in SOT or HSCT and the use of some medications in pregnancy are major concerns. The main components of brucellosis control programs are: animal vaccination, pasteurization of dairy products, health education of at risk populations and coordination between various governmental, regional and international organizations.

References

[1] Bosilkovski M (2014) Clinical manifestations, diagnosis and treatment of brucellosis. Up To Date. Topic edited by Calderwood SB, Edwards MS and Baron EL.
[2] Arizona Department of Health Services (2004) Brucellosis: Bioterrorism Agent Profiles for Health Care Workers, Office of Public Health Emergency Preparedness and Response 5.1 - 5.4.
[3] Young EJ (1995) An overview of human brucellosis. Clin Infect Dis 21: 283 - 289.
[4] Franco MP, Mulder M, Gilman RH, Smits HL (2007) Human brucellosis. Lancet Infect Dis 7: 775 - 786.
[5] Evans AS, Brachman PS (2009) Bacterial Infections of Humans Epidemiology and Control. (4th edition), Springer Science + Business Media, LLC, 233, New York, NY 10013, USA.
[6] Pappas G, Akritidis N, Bosilkovski M, Tsianos E (2005) Brucellosis. New Engl J Med 362: 2325 - 2336.
[7] Akhvlediani T, Clark DV, Chubabria G, Zenaishvili O, Hepburn MJ (2010) The changing pattern of human brucellosis: clinical manifestations, epidemiology and treatment outcomes over three decades in Georgia. BMC Infect Dis 10: 1 - 9.
[8] Christou L (2011) The global burden of bacterial and viral zoonotic infections. Clin Microbiol Infect 17: 326 - 330.
[9] Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos E (2006) The new global map of human brucellosis. Lancet Infect Dis 6: 91 - 99.
[10] Dean AS, Crump L, Greter H, Schelling E, Zinsstag J (2012) Global burden of human brucellosis: a systematic review of disease frequency. PLoS Negl Trop Dis 6: e1865.
[11] Mantur BG, Amarnath SK (2008) Brucellosis in India - a review. J Biosciences 33: 539 - 547.
[12] Seimenis A, Morelli D, Mantovani A (2006) Zoonones in the Mediterranean region. Ann Ist Super Sanità 42: 437 - 445.
[13] Hasanjani Roushan MR, Mohraz M, Hajihamdi M, Ramzani A, Valayati AA (2006) Efficacy of gentamicin plus doxycycline versus streptomycin plus doxycycline in the treatment of brucellosis in humans. Clin Infect Dis 42: 1075 - 1080.
[14] Mubyazi GM, Barongo VK, Kamugisha M, Njunwa KJ (2013) Public knowledge, perceptions and practices in relation to infectious and other communicable diseases in Tanzania: lessons learnt from Babati district. Rwanda J Health Sci 2: 1 - 12.
[15] Ariza J, Bosilkovski M, Cascio A, Colmenero JD, Corbel MJ, et al. (2007) Perspectives for the treatment of human brucellosis in the 21st Century: the Ioannina Recommendations. PLoS Med 4 e317.
[16] Cutler SJ, Fooks AR, van der Poel WH (2010) Public health threat of new, reemerging and neglected zoonoses in the industrialized world. Emerg Infect Dis 16: 1 - 7.
[17] Vassalo CM, Economou V, Vassalou E, Papadopaulor C (2009) Brucellosis in humans: why is it so elusive? Rev Med Microbiol 20: 63 - 73.
[18] Gwida M, Al Dahouk S, Melzer F, Rösler U, Neubauer H, et al. (2010) Brucellosis - regionally emerging zoonotic disease? Croat Med J 51: 289 - 295.
[19] Seleem MN, Boyle SM, Srivanganathan N (2010) Brucellosis: a re - emerging zoonosis. Veterinary Microbiol 140: 392 - 398.
[20] Russo G, Pasquali P, Nenova R, Alexandrov T, Ralchev S, et al. (2009) Reemergence of human and animal brucellosis, Bulgaria. Emerg Infect Dis 15: 314 - 316.
[21] Farina F, Fuser R, Rossi M, Scotton PG (2008) Brucellosis outbreak in Treviso province caused by infected cheese from an endemic area. Infez Med 16: 154 - 157.
[22] Nomura A, Imaoka K, Imanishi H, Shimizu H, Nagura F, et al. (2010) Human Brucella canis infections diagnosed by blood culture. Emerg Infect Dis 16: 1183 - 1185.
[23] Al - Anazi KA, Al - Jasser AM (2007) Brucella bacteremia in patients with acute leukemia: a case series. J Med Case Rep 1: 144.
[24] Eser B, Altuntas F, Soyuer I, Ozlem Er, Ozlem Canoz, et al. (2006) Acute lymphoblastic leukemia associated with brucellosis in two patients with fever and pancytopenia. Yonsei Med J 47: 741
[25] Kantartzi K, Panagoutsos S, Kokkinou V, Passadakis P, Vargemezis V (2009) Unexpectedly high incidence of brucellosis in one university dialysis unit of North East Greece. Nephrol Dial Transplant 24: 2003 - 2004.
[26] Ghanei E, Miladipour A, Nasrollahi A, Homayuni M (2009) Brucellosis with kidney failure. Iran J Kidney Dis 3: 109 - 111.
[27] Hajiabdolbaghi M, Rasoulinejad M, Abdollahi A, Paydary K, Valiollahi P, et al. (2011) Brucella infection in HIV infected patients. Acta Med Iran 49: 801 - 805.
[28] Moreno S, Ariza J, Espinosa FJ, Podzamczer D, Miró JM, et al. (1998) Brucellosis in patients with the Human Immunodeficiency Virus. Eur J Clin Microbiol Infect Dis 17: 319 - 326.

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[29] Ayyub M, Al - Juhani NR, Alfi AY, Al - Ukayli S. (2006) Brucellosis and dengue fever - a co - infection or cross reactivity? Biomedica 22: 80 - 83.
[30] Jacob NR, Rodríguez CG, Binaghi MA, Scapellato PG, Rosales Ostriz MB, et al. (2008) Brucellosis complicating chronic non - infectious disorders: diagnostic and therapeutic dilemmas. J Med Microbiol 57: 1161 - 1166.
[31] Akgul O, Ozgocmen S (2011) Infliximab and brucellosis: not the usual suspects, this time. Mod Rheumatol 21: 313 - 315.
[32] Eisele CW, McCullough NB, Beal GA (1950) Brucellosis and multiple sclerosis. J Am Med Assoc 143: 1473 - 1474.
[33] Murrell TG, Mathews BJ (1990) Multiple sclerosis - - one manifestation of neurobrucellosis? Med Hypotheses 33: 43 - 48.
[34] Jha A, Adhikari RC, Sarda R (2012) Bone marrow evaluation in patients with fever of unknown origin. J Pathol Nepal 2: 231 - 240.
[35] Mir T, Nabi Dhobi G, Nabi Koul A, Saleh T (2014) Clinical profile of classical Fever of unknown origin (FUO). Caspian J Intern Med 5: 35 - 39.
[36] Ergül N, Cermik TF (2011) FDG - PET or PET/CT in fever of unknown origin: the diagnostic role of underlying primary disease. Int J Mol Imaging 2011: 318051.
[37] Mete B, Vanli E, Yemisen M, Balkan II, Dagtekin H, et al. (2012) The role of invasive and non - invasive procedures in diagnosing fever of unknown origin. Int J Med Sci 9: 682 - 689.
[38] Neto AM, Corção G, Dasso MG, Keid LB, de Costa M (2014) Antimicrobial susceptibility profile of Brucella spp. isolated in Brazil. Rev Patol Trop 43: 163 - 172.
[39] Ayaşlioğlu E, Kiliç S, Aydin K, Kiliç D, Kaygusuz S, Ağalar C (2008) Antimicrobial susceptibility of Brucella melitensis isolated from blood samples. Turkish J Med Sci 38: 257 - 262.
[40] Tanyel E, Coban AY, Koruk ST, Simsek H, Hepsert S, et al. (2007) Actual antibiotic resistance pattern of Brucella melitensis in central Anatolia. An update from an endemic area. Saudi Med J 28: 1239 - 1242.
[41] Hashim R, Ahmad N, Mohamed Zahidi J, Tay BY, Mohd Noor A, et al. (2014) Identification and invitro antimicrobial susceptibility of Brucella species isolated from human brucellosis. Int J Microbiol.2014: 596245.
[42] Trujillano - Martín I, García - Sánchez E, Martínez IM, Fresnadillo MJ, García - Sánchez JE, et al. (1999) In vitro activities of six new flouroquinolones against Brucella melitensis. Antimicrob Agents Chemother 43: 194 - 195.
[43] Marianelli G, Ciuchini F, Tarantino M, Pasquali P, Adone R (2004) Genetic basis of the rifampicin resistance phenotype in Brucella spp. J Clin Microbiol 42: 5439 - 5443.
[44] Donev D (2010) Brucellosis Control and Eradication in the South Eastern European Countries: Current Status and Perspective Strategies. Macedonian J Med Sci 3: 220 - 228.
[45] Refai M (2002) Incidence and control of brucellosis in the Near East region. Vet Microbiol 90: 81 - 100.
[46] Hotez PJ, Savioli L, Fenwick A (2014) Neglected tropical diseases of the Middle East and North Africa: review of their prevalence, distribution and opportunities for control. PLoS Negl Trop Dis 6: e 1475
[47] Karaagac L, Koruk ST, Koruk I, Aksoy N (2011) Decreasing oxidative stress in response to treatment in patients with brucellosis: could it be used to monitor treatment? Int J Infect Dis 15: e346 - e349.

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