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Review Article

Brucellosis in Immunocompromised Hosts

Abstract

Recently, the incidence of brucellosis in immunocompromised patients has increased due to the parallel increase in the number of individuals with low immunity such as cancer patients and recipients of stem cell and solid organ transplantation. Additionally, the immunity of pregnant females is reduced and this makes them more susceptible to infections by various microorganisms including *Brucella* species.

In immunocompromised hosts, the clinical manifestations of brucellosis are very variable and complicated infections are prone to develop. Despite the recent progress in the diagnostics and therapeutics of brucellosis, interpretation of certain diagnostic tests in immunocompromised patients is occasionally difficult and treatment of the disease in this category of patients is also difficult due not only to adverse effects of the medications employed in the treatment of brucellosis but also to the interactions between antimicrobial therapies and immunosuppressive medications.

Abbreviations

HSCT: Hematopoietic Stem Cell Transplantation; SOT: Solid Organ Transplantation; RT-PCR: Real Time-Polymerase Chain Reaction; B.: *Brucella*; LPS: Lipopolysaccharide; IL: Interleukin; TNF: Tumor Necrosis Factor; HIV: Human Immunodeficiency Virus; CMV: Cytomegalovirus; H1N1: Swine Flu Virus; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; ESRD: End-Stage Renal Disease; DIC: Disseminated Intravascular Coagulation; MAHA: Microangiopathic Hemolytic Anemia; CNS: Central Nervous System; FUO: Fever Of Unknown Origin; EO: Epidedymo-Orchitis; ELISA: Enzyme-Linked Immunosorbent Assay; RA: Rheumatoid Arthritis; MLVA: Multi-Locus Variable Number Tandem Repeats Assay; FDG: Fluoro-18-fluoro-2-Deoxy-D-Glucose; PET: Positron Emission Tomography; CAT: Computerized Axial Tomography; BE: *Brucella* Endocarditis; MRI: Magnetic Resonance Imaging

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 [2]. The duration of the incubation period ranges between one week and several months. During this period of time, the clinical features are non-specific [1,3]. 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 [1,3]. 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 [1,3].

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 [4]. Therefore, sustaining a high index of suspicion is important as early diagnosis and prompt therapy improve the outcome and prevent complications [1,3,4].

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.

Incidence and epidemiology

Brucellosis is an infectious disease of animals (zoonosis) that is transmittable to humans by wild and domestic animals [5]. Several *Brucella* species have been identified, 6 of which are human pathogens [5-8]. The incidence of brucellosis varies considerably from time to time and from one country to another [9,10]. 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 [9,10].

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 [11-14]. In the era of globalization and international tourism, brucellosis has become a common imported disease in the developed world [9,15]. 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 [8,9,12]. Additionally brucellosis is a notifiable disease in most countries [17].

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The epidemiology of human brucellosis has changed over the last 25 years [9,10]. Unfortunately, in many *Brucella*-endemic countries, the health systems are weak and official data are likely to underestimate the true burden of the disease [10]. 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 survival which is mainly attributed to the recent improvements in medical care [9,10,18-21].

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 [2,7,9,10,17,22,26]. Brucellosis is an occupational disease that poses risk to shepherds, abattoir workers, veterinarians and personnel working in diary-industry and microbiology laboratories [2,7,26]. 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) [2,7,23-25,27,32].

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* [5-8]. 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 [33]. 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 [33].

Seroprevalence and blood transfusion-related brucellosis

Several studies on seroprevalence of brucellosis in high risk human populations in countries which are endemic for the disease have shown that the seroprevalence figures are as follows: 8.8% in Kyrgyzstan; 2.2-21.6% in Bangladesh; 6.9% in Pakistan; 24.1% in Nigeria; 27.3% in Mongolia and 15% in Saudi Arabia [34-39].

Blood transfusion as a means of transmission of brucellosis in recipients of blood product transfusions had been reported since the year 1950. Screening of blood donors for brucellosis has revealed that *Brucella* antibodies are present in the serum samples of 0.06% to 3.2% of blood donors [27,28,32]. Although brucellosis is a blood-borne pathogen, there have been either rare or no reports of blood transfusion-transmitted brucellosis in certain countries that are endemic for brucellosis [40]. However, in a study performed in China in which 3896 plasma samples had been collected, 15 blood donations, that is, 1:300 cases were found to be positive by nucleic acid testing and they were confirmed by DNA sequencing [41]. The data indicate that a probable high rate of *Brucella* bacteremia suggesting a potential risk of transfusion transmitted brucellosis. Therefore, screening of donated blood for *Brucella* infection should be considered in highly endemic geographic locations [41].

Although the prevalence is not high, brucellosis could be a risk for blood transfusion and blood donors coming from rural areas in endemic geographic locations should be screened for brucellosis [42]. Also, they should be asked about consumption of unpasteurized milk and dairy products as well as contact with infected animals [42]. In a Turkish study that included 632 volunteers for blood donation, 4 donors had positive serology for brucellosis and *Brucella* species was detected by right time (RT)-PCR in 2 donors [42]. However, the clinical manifestations of bacterial sepsis due to *Brucella* infection related to blood transfusion may include: fever, rigors, tachycardia, hypotension, nausea, vomiting, dyspnea and back pain [40].

Pathogenesis of brucellosis

The pathogenicity of human brucellosis is attributed to factors such as lipopolysaccharide (LPS), adenine and guanine monophosphate, vitamin B, 24 KDa protein and urease enzyme [11]. In the past decade, the mechanisms of *Brucella* pathogenesis and host protective immunity against *Brucella* infections have been extensively investigated using cutting edge systems biology and bioinformatics approaches [43]. The persistence of bacterial colonization in the cells of the reticuloendothelial system is an important feature of brucellosis [44]. The ability of some *Brucellae* to survive the reactive oxygen intermediate and the nitric oxide killing in the host phagocytes results in the chronicity of brucellosis [45].

Production of interferon-γ (IFN-γ) results from the ability of *Brucella* components, including lipid A, to interact with Toll-like receptors for the production of interleukin (IL)-12 and tumor necrosis factor (TNF)-α, although the regulatory cytokine IL-10 is also produced and decreases control of the infection [45].

IFN-γ is a crucial component of immunity that limits intracellular replication of various *Brucella* species thus maintaining a chronic infective state in the host [45].

Three mechanisms are involved in the immune response to brucellosis: (1) interferon-γ activates the bacterial function in macrophages to hamper the intracellular survival of *Brucella*

species, (2) cytotoxicity of $CD8_+$ and $\gamma\delta T$ cells destroy the infected macrophages, and (3) Th_1-type antibodies opsonize the pathogen to facilitate phagocytosis [46]. The granulomatous response is a characteristic feature of *B. abortus* infection. In *B. melitensis*, the granulomata are very small while *B. suis* infection is associated with chronic abscess formation [46]. LPS has a role in cell entry and immune evasion of the infected cell and is essential for intracellular survival. *Brucella* species invade and persist in the host via inhibition of programed cell death and replication of the bacterium takes place in the endoplasmic reticulum [46]. The human host response is both humoral and T-cell mediated, although cell mediated immunity appears to be the principal mechanism of recovery. Antibodies are important for diagnostic purposes but appear to play a minor role in the immune response to infection [46]. It is well established that infection with some intracellular bacteria may have an indirect effect on the immune system, thus ultimately leading to immunosuppression. Among the leading bacterial causes of immunosuppression are *B. melitensis* and *Mycobacterium tuberculosis* [47]. Survival of *Brucella* species within monocytes is the single most important aspect of pathogenesis contributing to persistence of the bacteria in host tissues [48].

Recently, molecular studies have highlighted the pathogenesis of *Brucella* species and this will accelerate the development of new diagnostic techniques that are useful in developing countries where brucellosis, despite being common, is often neglected [49]. Genetic studies have shown that *B. abortus* and *B. melitensis* share the same lineage and differ from *B. suis* which has undergone few genetic mutations and has diverged from the most recent ancestor of all *Brucellae* [49]. Increased serum levels of IL-6, IL-8 and IL-12 have been reported in patients with brucellosis, while IL-8-251AA and rs3212227AA genotypes have been found to increase the genetic susceptibility to acquire *Brucella* infections [50,51]. Additionally, the neutrophil/lymphocyte ratio in the blood has been found to be significantly associated with *Brucella* infection in humans [52].

Virulence of *Brucella* species

Although *Brucella* does not bear classic virulence factors, the organism tends to invade and persist in human hosts [6]. Virulence of *Brucella* species relies on the ability of the organism to survive and replicate in the in the host cells [43,53]. Although these virulence factors are critical for replication of the organism inside host cells, they may not directly mediate the clinical manifestations of brucellosis [53]. Several *Brucella* virulence factors have been identified and they include: (1) LPS, (2) type 4 secretion systems (T4SSs), and (3) the BvrR/BvrS two-component system [43,54,55].

Secretion of proteins across membranes is of vital importance in bacterial virulence [54]. The T4SSs are membrane-associated transporter complexes that are used by various bacterial species to deliver substrate molecules to a wide range of target cells and they contribute to the following important processes: (1) exchange of genetic material, (2) bacterial colonization and biofilm formation, and (3) injection of virulence factors into the host cytoplasm [54]. Several lines of evidence indicate that the role of virulence in *Brucella* species is important [54]. The T4SS, which is encoded by the virB locus, is located on chromosome 2. The *Brucella* species

T4SS, encoded by virB1and virB12 locus, is required for intracellular replication and persistent infection in vivo [55]. During infection in both experimental animals and natural hosts of *Brucella* species, virB12 is expressed, so it may be a useful serodiagnostic marker of brucellosis [55]. Additionally, antibodies to *B. abortus* virB12 have been identified in mice, goat and cattle. Therefore, detection of humoral responses to virB12-specific immune responses can be used in the diagnostic algorithm of human brucellosis [55]. *B. microti* exhibits a high pathogenic potential in experimental murine infections [56]. Lethality of *B. microti* in murine infections primarily requires a functional virB12 operon [56]. The T4SS, encoded by virB operon, is the most-studied and best-characterized virulence factor of *Brucella* species [56].

During the past decade, systems biology and bioinformatic approaches have been widely used to: (1) study the mechanisms of *Brucella* pathogenesis and host protective immunity against *Brucella* infections, and (2) support vaccine design [43]. Based on more than 30 sequenced *Brucella* genomes, comparative genomics is able to identify gene variations among *Brucella* strains that help to explain host specificity and differences in virulence among *Brucella* species [43]. More than 180 virulence factors and their gene interaction networks have been identified using advanced literature mining methods [43].

Clinical manifestations of brucellosis

The incubation period of brucellosis is usually 1-4 weeks, but may be as long as several months [1]. Generally, *B. melitensis* causes more severe infections than *B. abortus*, *B. suis* causes human infections that are as severe as those caused by *B. melitensis*, and *B. canis* which is infrequently encountered in humans causes mild disease [1].

High grade, irregular fever which has insidious onset and that lasts for days to weeks is the commonest clinical feature. However, brucellosis may present as fever of unknown origin (FUO) and the infection may occasionally be atypical [1,11]. The other clinical features of brucellosis include: night sweats, chills and rigors, anorexia, malaise, weakness, weight loss, headache, arthralgia, myalgia, low backache, dizziness, depressed mood, dyspepsia, nausea, vomiting, abdominal pain, cough, dyspnea, epistaxis and hemoptesis, burning micturition, testicular pain, swollen and tender joints, tenderness over the lumbosacral spine, splenomegaly, hepatomegaly, external lymphadenopathy, jaundice, mouth ulcerations, scrotal swelling in addition to various cutaneous eruptions [1-5,9-11,22,57,-61]. In a study performed in Saudi Arabia that included 73 episodes of brucellosis in 55 patients, 44% of the patients had rheumatic manifestations such as arthritis and spondylitis [62]. Brucellosis can have several presentations and the disease has several stages: acute, sub-acute, chronic, relapsing, active and non-active. Therefore, discriminatory, diagnostic as well as prognostic markers, particularly for monitoring disease activity are ongoing. Also, despite the progress that has been achieved, several challenges remain [63].

Cardiovascular complications of brucellosis

Cardiovascular complications occur in approximately 1%-2% of patients with brucellosis [64-67]. Cardiac complications of *Brucella* infection include: endocarditis, myocarditis, pericarditis, pericardial

effusions and heart failure. Pericarditis, myocarditis and pericardial effusions can be encountered in the absence of endocarditis [65,66,68,69]. Also, isolated cases of *Brucella* myopericarditis have been reported [67].

Brucella endocarditis (BE) occurs in less than 2% of patients with brucellosis, but it is serious and may be life-threatening [68,70-72]. BE can affect native or prosthetic heart valves and the aortic valve is involved in 75% of cases. Underling pathologies, such as rheumatic heart disease or degenerative heart valves, are usually present [68,70-72]. The clinical manifestations of BE include: fever, dyspnea, fatigue, weight loss, a new heart murmur and valve dysfunction or regurgitation in addition to external palpable lymphadenopathy and hepatosplenomegaly [68,70-72]. BE can be complicated by: annulus abscess, pericarditis, congestive cardiac failure, septic emboli and death [68,70,71]. BE is the main cause of death in patients with brucellosis and mortality rate due to BE is about: 20%-30% [68,72]. Blood cultures are usually positive in 17%-85% of patients with BE [70,71]. Echocardiographic findings include: valve dysfunction, vegetations, ulcerations and abscess formation [70,71]. BE can be treated by: (1) surgical intervention in the form of valve replacement, and (2) antimicrobial therapy which should be administered for 3 weeks before surgery in order to ensure hemodynamic stability and achievement of sterilization before surgical therapy [68,70-72]. Post-operatively, BE patients require prolonged courses of antimicrobial therapy. The following antibiotics have been utilized in the treatment of BE: doxycycline or tetracycline, rifampicin, streptomycin and ceftriaxone [68,70-72]. In patients with BE, who are hemodynamically stable and having no complications, combinations of antimicrobials may be sufficient and may rule out the need for surgical intervention [72]. A high degree of suspicion is required in areas that are endemic for brucellosis [68,71].

Brucella pericarditis is very rare [66]. It may be almost asymptomatic or may cause cardiac tamponade [67]. The following lines of management are usually undertaken: pericardiocentesis, antibiotics and symptomatic treatment in the form of analgesics and anti-inflammatory drugs [66]. Pericardiocentesis should only be performed in patients with cardiac tamponade [66,67]. Although *Brucella* pericarditis is usually associated with low morbidity and mortality, it should always be kept in mind in patients with acute or chronic pericarditis particularly in individuals living in areas that are endemic for brucellosis [66].

Brucella myocarditis is also a very rare complication of brucellosis and only few cases have been reported in literature [64,69,73]. It may be complicated by heart failure [69]. Severe myocarditis complicating acute brucellosis may be fatal [64]. *Brucella* myocarditis may occur in isolation or as part of disseminated *Brucella* infection [64]. Patients with *Brucella* myocarditis usually experience prolonged pyrexia, high C-reactive protein and delayed enhancement of cardiac ventricular walls on magnetic resonance imaging (MRI) [73]. Combination of doxycycline and rifampicin for 3 months may be curative [73]. However, early diagnosis and prompt initiation of appropriate antimicrobials are essential to prevent complications of *Brucella* myocarditis [64].

Neurobrucellosis

Both central and peripheral nervous systems can be affected by brucellosis [74]. Central nervous system (CNS) involvement, although uncommon, is a serious complication of brucellosis. It has been reported in 1.7% -11% of patients with brucellosis [74-78]. Neurobrucellosis presents in a heterogeneous manner and the clinical manifestations and complications may include: fever, headache, nausea, vomiting, sweating, weakness, weight loss, back pain, neck stiffness, hearing loss, mental confusion, coma, convulsions, depression, dementia, papilledema, optic neuropathy, stroke, paraplegia, motor deficits, polyneuropathy, radiculopathy, cranial nerve palsies, pseudotumor cerebri, hydrocephalus, subarachnoidal hemorrhage, subdural hematoma, sagittal sinus thrombosis, intracranial vasculitis, spinal arachnoiditis, brain or paraspinal abscess, meningitis, encephalitis, transverse myelitis, hepatosplenomegaly and death [74-78].

Blood investigations usually show: leucopenia or leukocytosis, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [77]. Cerebrospinal fluid (CSF) analysis usually shows: lymphocytic pleocytosis, high protein, low glucose, positive cultures and positive CSF Brucella serology [74,75,77,78]. Computerized axial tomography etc. (CAT) scans and MRI of brain and spinal cord may show: space occupying lesions such as granulomas or abscess formation and white matter lesions with demyelination [74,77,78]. Neurobrucellosis should be differentiated from: neurosyphilis, neurotuberculosis and other causes of purulent meningitis [75].

For *Brucella* meningitis, initially parenteral third generation cephalosporin such as ceftriaxone should be given, followed by various combinations of antimicrobials including: doxycycline, rifampicin, streptomycin or trimethoprim-sulfamethoxazole (TMP/SMZ) [74,75,77]. The duration of antimicrobial therapy varies between 2 and 17 months with a median duration of 5 to 6 months [75-77]. However, treatment should be individualized according to the complications encountered [75]. Neurobrucellosis is rarely fatal provided the diagnosis is made early and appropriate therapy is administered promptly [74,76]. With appropriate treatment, mortality due to neurobrucellosis is approximately 0.5%, while untreated neurobrucellosis is associated with high morbidity and mortality [74-76] Physicians working in geographic locations that are endemic for brucellosis should maintain a high index of suspicion and should consider neurobrucellosis in patients presenting with unexplained neurological manifestations or psychiatric symptoms [74,77,78].

Other serious complications of *Brucella* infection

Rare but potentially life-threatening complications of brucellosis include: (1) disseminated infection with nodules and abscesses in the liver, spleen, gall bladder, lung, pleura and spine, (2) pancytopenia combined with endocarditis or meningitis, and (3) *Brucella* bacteremia that may cause septic shock [79-82]. Complicated infections are more likely to occur in immunocompromised hosts and require prompt diagnosis and early institution of appropriate therapy that includes surgical drainage, antimicrobial chemotherapy, artificial ventilation and transfusion of blood products [79-82].

Relapse of brucellosis:

Relapses occur in up to 29% of patients with brucellosis and

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they usually occur within 12 months of discontinuation of the antimicrobial therapy [1,3,5,58,62]. The risk factors for relapse include: male sex, old age, lymphopenia, deficient immunologic response such as in patients having *human immunodeficiency virus* (HIV) infection, presence of an aggressive disease or a chronic infection, positive blood cultures during initial infection, and an inadequately treated infection [1,3,5,83-86]. The laboratory findings in relapsing brucellosis are positive blood cultures in addition to elevation of the erythrocyte sedimentation rate (ESR) as well as CRP [3,15,84]. Most relapses can be successfully treated with longer courses of the standard therapeutic regimens and surgical intervention in case of localized foci of infection [1,3,5,58].

Chronic brucellosis:

Chronic brucellosis traditionally refers to the persistence of clinical manifestations for at least one year after establishment of the diagnosis of brucellosis [1,3]. It is characterized by: (1) localized infection such as spondylitis or osteomyelitis, (2) relapse in patients with an objective evidence of infection and (3) manifestations such as chronic fatigue syndrome and psychoneurosis [1,3,5]. The diagnosis of chronic brucellosis should be established on clinical grounds and history of the illness [1,87-92].

Reactivation of old *Brucella* infections

Reactivations of old *Brucella* infections have been reported 28 and even 70 years after the primary infection [93,94]. The risk factors for reactivation of old brucellosis include: old age, malignancy such as lymphoma, chronic medical illness such as hepatitis C, cytotoxic chemotherapy and immunosuppressive agents such as interferon [93-95].

Recovery of *Brucella* species from old human remains

Ancient skeletal remains can harbor unique information about past civilizations at both morphological and molecular levels. The occurrence of brucellosis in archaeologically recovered human bones, belonging to 2 young patients who lived in Albania between the 10th and 13th centuries, has been confirmed using DNA sequencing technology [96]. Also, 6 old cases of brucellosis with skeletal involvement belonging to the period between the 5th and 12th centuries have been recovered from Western Europe Mediterranean countries using molecular techniques such as PCR.

The recovery DNA sequence of a certain pathogen from human remains provides an opportunity to identify and characterize the causes of individual and epidemic infections [97]. Shotgun metagenomics provide an approach to recover pathogen genomes from historical material [98]. The DNA, which had been extracted from medieval human remains using shotgun metagenomics, was sequenced and a draft genome sequence of a 700-year-old *B. melitensis* strain was obtained [98]. Bioinformatic approaches showed that the historical strain is most closely related to the recent *B. melitensis* strains isolated from Italy [98].

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 [99-112].

Brucellosis in solid organ transplantation (SOT)

Currently, SOT that includes transplantation of kidney, lung, heart, liver, pancreas and small bowel is the treatment of choice for many end-stage diseases [104,113]. Since the first successful kidney transplantation in 1954, SOT has increased worldwide as currently more than 70,000 SOTs are performed annually [113,114].

As a consequence of improved immunosuppressive therapy and graft survival, infection and malignancy have become the main barriers to disease free survival after SOT [114]. Infectious causes remain a major complication in SOT recipients as they are associated with significant morbidity and mortality [104]. However, the risk of transmission of an infectious agent from the organs obtained from deceased or cadaveric donors is less than 1% [104]. As a result of growing population of immunocompromised hosts and prolonged survival of these patients, a recent increase in the incidence and spectrum of opportunistic infections has been observed [114]. The risk of infection in recipients of SOT is mostly related to: (1) the epidemiological exposures of the individual, and (2) the net state of immunosuppression [104,114]. The net state of immunosuppression is determined by interaction of the following: (1) the type, dose and duration of immunosuppressive therapy administered, (2) the underlying disease and the comorbid medical conditions, (3) presence of devitalized tissues or fluid collection in the transplanted body organ, (4) presence of indwelling devices such as central venous catheters, (5) other host factors that increase the susceptibility to infections such as: neutropenia, hypogammaglobulinemia, diabetes mellitus, uremia, malnutrition, and (6) concomitant viral infections such as *Epstein-Barr virus* and *cytomegalovirus* (*CMV*) [114].

Immunosuppression following SOT enhances the risk of infection by: (1) increasing the risk of tissue invasion, (2) increasing the risk of dissemination and superinfection, and (3) blunting or masking the typical inflammatory responses that are usually encountered in immune competent individuals [104]. Related to the risks of infection by specific microorganisms, the post-transplant period is divided into three periods: (1) the early post-transplant period (the first month), (2) the intermediate post-transplant period (1-6 months) and (3) the late post-transplant period which is the time when the transplant recipients suffer the greatest impact of immunosuppression and consequently are at the highest risk of developing opportunistic infections [114].

Pre-transplant screening and evaluation

Pre-transplant screening of potential donors and recipients of SOT is essential to the success of SOT [115]. Diagnostic testing and management of infectious complications in recipients of SOT must be guided by: (1) culture of the organism from various sites in addition

to tissue histology, (2) serological tests which indicate exposure to pathogens, and (3) vulnerability of SOT recipients to infections with drug-resistant organisms [114]. The goals of pre-transplant infectious disease screening are: (1) identification of conditions that may disqualify the donor or the recipient, (2) identification and treatment of active infections in the pre-transplant period, (3) definition of the risk of infection, and (4) implementation of appropriate preventive interventions [115].

Pre-transplant evaluation should include inquiry about history of: (1) specific infections and the treatments administered, (2) travel, (3) environmental exposures, (4) animal exposures in case of zoonotic infection such as brucellosis, and (5) infection prevention approaches and updating of immunization [115]. Health education and provision of printed material are essential in the prevention strategies of infections [115]. Absolute prevention of the transmission of donor-derived infections in SOT is not possible, but improvement in screening technologies will enhance the safety of SOT in the future [113]. Future advances will likely include: (1) the utilization of rapid molecular diagnostic procedures particularly for fastidious organisms such as *Brucella* species, and (2) possibly, additional testing for newly emerging pathogens such as *Swine Flu virus* (*H1N1*) and *Corona virus* infections [115].

Donor-derived infections:

Donor-derived infections can be acquired if the donor has any bloodstream infection at the time of donation [114]. However, there is general agreement on screening for major infections, but there is some variation between transplant centers regarding the type of screening used and the action to be taken once the results of screening are available [115].

The risk of transmission of infection by the allograft is largely unknown and can be difficult to assess for a specific organ that is donated. The approach to screening of organ donors varies according to the: (1) national and regional regulations, (2) availability of certain microbiological assays or tests in the transplantation center, and (3) epidemiology of infections in the region, particularly endemic infections such as brucellosis [113]. The infections that can be transmitted by SOT are included in Table 1, [104,105,114-117].

Post-transplant infections

The goals of patient care following SOT are: (1) prevention of transmission of donor-derived infections, (2) early recognition of infections in recipients of SOT, and (3) early intervention once an infection is strongly suspected [104]. The diagnosis and treatment of infectious complications following SOT are often delayed because: (1) presentation of infection may be atypical, and (2) presentation of infection may be complicated by allograft rejection [104]. It is desirable to obtain blood cultures from living SOT donors and once positive blood cultures are obtained, thorough investigations should be performed, with particular attention paid to endemic infections such as brucellosis [104].

Infectious pathogens may be carried by the graft or by transfusion of blood products during or after transplantation [117]. Transmission of tropical infectious diseases occurs through 3 main routes: (1)

donor-derived infections, (2) reactivation of old or latent infections such as tuberculosis or brucellosis, or (3) de novo transmission occurring during the post-transplant period. Also, infections caused by bacterial pathogens can occur once corticosteroids, mycophenolate mofetil and rituximab are prescribed [114,117].

Tropical infections in SOT recipients

The risk of acquiring tropical infectious diseases varies with: (1) the destination of travel, (2) the type of exposure, (3) the purpose of the trip, (4) the level of accommodation, hygiene and sanitary level, and (5) the behavior of the transplant traveler [105]. The number of reports of tropical infections in SOT recipients is growing due to: (1) increasing travel of transplanted recipients to the tropics and subtropics, (2) increasing immigration of populations from endemic areas for tropical infections to non-endemic areas, (3) increasing numbers to transplantation procedures taking place in tropical countries, and (4) transplant tourism as many patients travel overseas to countries having high prevalence of tropical diseases [105]. It is essential to encourage SOT recipients travelling to high-risk areas to seek expert advice regarding preventive strategies and vaccines [105]. Some tropical infectious diseases may increase the risk of organ transplant rejection [105]. Uncomplicated as well as complicated infections, such as *Brucella* endocarditis and neurobrucellosis, have been reported in recipients of SOT [105,118,119].

Reported cases of brucellosis in recipients of SOT

Brucellosis has been reported in recipients of SOT. However, it is more frequent in renal transplant recipients than in recipients of liver transplantation. Brucellosis can develop as early as 2 months and as late as 17 years post SOT [105,117,118,120-123]. The sources of *Brucella* infections in recipients of SOT include: (1) donor-derived infection, (2) blood transfusion-related infection, (30 reactivation of old infection due to the immunosuppressive therapy administered to prevent graft rejection, and (4) new infection in these patients who are vulnerable to various infectious complications due to their immunocompromised status [105,118,122-125].

The following complications have been reported in SOT recipients: *Brucella* arthritis, neurobrucellosis, paraspinal abscess, *Brucella* endocarditis, *Brucella* bacteremia in addition to hematological and hepatobiliary complications [105,118,120-123]. Brucellosis in recipients of SOT responds well to various combinations of the following antimicrobials: doxycycline, rifampicin, ciprofloxacin and TMP/SMZ. However, complicated infections may require not only prolonged courses of antimicrobials for 6 to 12 weeks but also surgical intervention, particularly in the presence of BE or abscess formation [117,120,121,123]. Tigecycline is a potential therapeutic option in the treatment of brucellosis in SOT recipients [123]. Drug interactions between antimicrobials and immunosuppressive therapies have to be taken into consideration in recipients of SOT being treated for brucellosis [123].

Prevention of infections in SOT

The risk of donor-derived infection can be reduced by: (1) improving donor screening, (2) analysis of exposure history, and (3) acquiring advanced molecular biology-based diagnostic testing

Table 1: Infections transmitted by SOT and HSCT.

Type of infection	SOT		HSCT
Bacteria	- *Staphylococcus aureus* - *Klebsiella* species - *Bacteroides fragilis* - *Pseudomonas aeruginosa* - *Escherichia coli* - *Yersinia enterocolitica*	- *Salmonella* species - *Brucella* species - *Bartonella* species - *Enterobacter* species - *Acinetobacter* species - *Treponema pallidum* - *Leptospira* species	- Contaminants - *Brucella* species
Fungi	- *Candida* species - *Aspergillus* species - *Histoplasma capsulatum* - *Cryptococcus neoformans* - *Coccidioides immitis* - *Scedosporium apiospermum* - *Prototheca* species.		- *Candida* species - *Aspergillus* species
Mycobacteriae	- *Mycobacterium tuberculosis* - *Mycobacterium leprae* - Non-tuberculous *Mycobacteriae*		- *Mycobacterium tuberculosis* - *Mycobacterium leprae* - Non-tuberculous *Mycobacteriae*
Parasites and protozoa	- *Plasmodium* species - *Schistosoma* species - *Giardia lamblia* - *Taenia solium* - *Entamoeba histolytica*	- *Wuchereria bancrofti* - *Toxoplasma gondii* - *Trypanosoma cruzi* - *Strongyloides stercoralis* - *Pneumocystis jiroveci pneumonia*	- *Pneumocystis jiroveci pneumonia* - *Plasmodium* species - *Toxoplasma* species - *Babesia* species - *Leishmania* species
Prions	--------------		• Creutzfeld-Jacob disease
Viruses	- *Cytomegalovirus* - *Epstein-Barr virus* - *Adenovirus* - *Influenza virus* - *Parainfluenza virus* - *Metapneumovirus* - *Varicella-zoster virus* - *Herpes Simplex virus* - *Parvovirus B$_{19}$ virus* - *Rabies virus* - *Dengue virus* - *West Nile virus*	- *Hepatitis viruses*: B,C and D - *SARS, Corona virus* - *Respiratory syncytial virus* - *Human immunodeficiency virus* - *Human T cell lymphotrophic virus* - *Lymphochoriomeningitis virus* - *Human Herpes viruses*: 6,7 and 8	- *Cytomegalovirus* - *Epstein-Barr virus* - *Human T cell lymphotrophic virus* - *Human immunodeficiency virus* - *Hepatitis viruses*: B,C and D - *Respiratory syncytial virus* - *Adenovirus* - *Parvovirus B19* - *West Nile virus* - *Metapneumovirus* - *Influenza virus* - *Parainfluenza virus*
SOT: solid organ transplant HSCT: hematopoietic stem cell transplantation			

[117]. Occupational exposure should be avoided, particularly during the first 6 months after transplantation [117]. Education of transplant recipients before and after transplantation regarding zoonotic risks may further decrease zoonotic infection in these immunocompromised individuals. Unfortunately, the live-attenuated *Brucella* animal vaccine has the potential to cause disseminated disease in immunocompromised humans [117].

Brucellosis in recipients of HSCT

Transmission of bacteria to a recipient of HSCT usually occurs through: (1) contamination of the graft, (2) blood of the donor, (3) bone marrow of the donor, and (4) blood product transfusions in the post-HSCT period [29,57,100,105,116-118,126-128]. The reported contamination rates of about 1 per 3000 units as observed in blood products seem to be excessive in the absence of definitive information and data from other studies [116]. Cryopreserved autologous grafts or cord blood may be contaminated with Gram-positive bacteria or less frequently with Gram-negative bacteria [116]. With the increase in donor age, the potential of transmitting diseases from donors to recipients reaches new dimensions [116]. The potentially transmittable diseases from HSCT donors include: (1) infections caused by various micro-organisms as shown in Table 1, [104,105,113,115-117], (2)

congenital diseases such as thalassemia, (3) autoimmune disorders such as autoimmune thrombocytopenia, and (4) malignancies such as leukemia and lymphoma [116]. Donor-derived infections caused by viruses, fungi, parasites, *Mycobacteriae* and several other bacteriae including *Brucella* species have been reported in recipients of HSCT [104,105,113,115-117,126-128]. One of the prerequisites for donating hematopoietic stem cells is to have a healthy donor who will pass all screening tests for various infections [128]. Once a certain infection is diagnosed in a potential donor for HSCT, it has to be treated appropriately before reconsidering the donor again [128]. Identification of donors at high risk of transmittable infections is essential and HSCT donors should have thorough evaluation and detailed history [116]. Brucellosis is not routinely screened for in the western countries, but donor screening for brucellosis is of vital importance in endemic areas [116]. Evaluation of donor-transmitted complications within the established registries is urgently needed and systemic monitoring of incidence, severity and outcome of donor related complications including infections is essential [116].

Most zoonotic infections occur as a primary infection after transplantation and hence immunocompromised individuals are likely to experience significant morbidity and mortality [117]. Donors

and recipients of HSCT are at risk of acquiring zoonotic infections such as brucellosis due to immigration, foreign travel and exotic pets [117]. Detailed medical history including risk factors for *Brucella* infection should be obtained during the pre-donation period of time and before clearing the donor [127]. *Brucella* serology is usually performed during the period of donor evaluation within at least 30 days prior to stem cell donation [127]. Brucellosis in a donor of HSCT should be treated and the donor should not be allowed to donate stem cells till at least two years after full recovery from the infection [128]. *Brucella* infections have been: (1) transmitted to recipients of HSCT through allografts harboring *Brucella* species, and (2) reported in recipients of HSCT after achieving successful engraftment [29,57,100,105,116-118]. In recipients of HSCT living in endemic areas, brucellosis and *Brucella* bacteremia can develop at any stage of their illness [29,100,126]. In these patients, brucellosis usually presents with fever and various degrees of cytopenias [100]. The administration of appropriate antimicrobials will control the infection and prevent further complications [100]. Although brucellosis can be treated successfully with antibiotics, donors and recipients living in endemic areas should be appropriately screened for brucellosis [116].

Brucellosis in pregnancy

In endemic areas, the cumulative incidence of brucellosis in pregnant women may reach 1.3 per 1000 obstetric deliveries [38,129]. Brucellosis in pregnancy can present in an acute, subacute or a chronic manner [106]. The clinical manifestations of brucellosis in pregnant females are similar to those in the general population [129]. Occasionally, it may be complicated by *Brucella* bacteremia, septic shock, neurobrucellosis and disseminated intravascular coagulation (DIC) [131,132]. Brucellosis in pregnancy may predispose to spontaneous abortion, intrauterine fetal death, premature delivery, low birth weight in addition to postpartum intrauterine infections [1,130,133-139]. Vaginal bleeding at presentation may be an early sign of spontaneous abortion. Unfortunately, delivery of pregnant women having brucellosis may cause infection of the delivery team [38,138].

Presence of carbohydrate erythritol in the animal placenta appears to be a preferential growth medium for *Brucellae* in animals. Consequently, brucellosis causes fewer spontaneous abortions in humans than in animals [132,140]. The presence of anti-*Brucella* activity in the amniotic fluid and the absence of erythritol in human placenta are believed to protect against abortion. Nevertheless, positive *Brucella* cultures have been obtained from the products of conception such as the human placenta and the aborted fetuses [137,140]. In pregnant females having brucellosis and living in areas that are endemic for the disease, the incidence of spontaneous abortion ranges between 24% and 53% while positive *Brucella* serology may be encountered in less than 3% of pregnant women [38,130,134]. *Brucella* seropositivity is not more common in women with spontaneous abortion or miscarriage than in women with uncomplicated pregnancies [141,142]. Some studies have shown that there is no correlation between the magnitude of *Brucella* agglutination titer and the occurrence of spontaneous abortion while others have shown that *Brucella* titers higher than 1:160 are associated

with higher probability of spontaneous abortion [38,130,136,143].

Brucellosis in pregnancy should be treated as soon as the diagnosis is made so as to prevent the evolution of complications [130,133,137]. There are no randomized trials on the treatment of brucellosis in pregnancy, but the combination of TMP/SMZ and rifampicin is the most commonly used regimen [1,130,134,137]. Nevertheless, brucellosis in pregnancy has been successfully treated with single agents such as rifampicin or TMP/SMZ, although monotherapy is usually associated with high relapse rates [38,133,138,141,144]. The optimal duration of antimicrobial therapy is 6 weeks and the success rate of antibiotic treatment for brucellosis in pregnant women may reach 90% [129,138,141]. Screening programs for brucellosis in pregnant women living in endemic areas and health education of the target populations are recommended [141,142,145]. Brucellosis should be included in the differential diagnosis of fever in pregnant females living in endemic [141,142].

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 [99,106-109,146-150]. 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 [61,99,106-109,150,151] 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 [147-149,152-156]. Brucellosis may develop at presentation of the hematological malignancy or even if the disease is under control [99,150,151]. Presentation of brucellosis is usually with fever and pancytopenia, although some patients may present with clinical manifestations similar to those in immunocompetent individuals [99,106,107,146,150,151]. Early diagnosis of brucellosis and prompt administration of appropriate antimicrobial therapy usually improve the outcome in such immunocompromised individuals [99,150,151]. 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 [99,150,151].

Brucellosis and renal disease

Brucellosis has been reported in patients with end stage renal disease (ESRD) living in endemic areas [157,158]. Presentation is usually with FUO but the infection may be complicated by neurobrucellosis, paravertebral and epidural abscesses and peripheral arthritis [157,158]. Brucellosis has been reported to cause ESRD, pyelonephritis, interstitial nephritis, mixed cryoglobulinemia and IgA nephropathy [159]. 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 [159]. Antimicrobial therapy given for brucellosis usually improves

the renal involvement [159].

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 [86,160-166]. The risk factors for *Brucella* infection in HIV patients are male sex and intravenous drug abuse [162,163]. 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 [163]. 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 [1,162].

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 [95,166-171].

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 [172,173].

Approximately 40% of patients having brucellosis develop systemic and chronic manifestations similar to those of chronic fatigue syndrome or myalgic encephalomyelitis [101]. 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 [102,174,175].

Brucellosis and solid tumors

It has been postulated that tumor formation might be associated with chronic brucellosis [103]. The DNA of *Brucella* species has been identified in CNS tumors such as medulloblastomas. Therefore, further studies are required to explore the true association between tumor formation in the CNS and the DNA positivity of *Brucella* species [103]. In patients having brucellosis and solid tumors, treatments of both brucellosis and the primary cancer should be administered to control both disorders [176].

Brucellosis may coexist not only with solid tumors but also with other infections such as tuberculosis as the clinical and radiological manifestations of cancer and chronic infections may overlap [103,110,111,176]. Brucellosis has been reported to coexist with the following solid tumors: (1) medulloblastoma and glioblastoma

multiforme as both can resemble neurobrucellosis, (2) lung carcinoma as pulmonary tuberculosis and respiratory brucellosis can give rise to similar lesions, (3) ovarian cancer as tubo-ovarian brucellosis can give rise to similar manifestations, (4) prostatic cancer as brucellosis can cause prostatitis, prostatic swelling and abscess formation, and (5) hepatocellular carcinoma as brucellosis can cause single and multiple hepatic nodular lesions [103,110,111,176,177]. However, the following can help in differentiating brucellosis from solid tumors: (1) the clinical manifestations based on careful and detailed history as well as comprehensive physical examination, (2) positive serological testing for brucellosis, although serological tests may not be entirely reliable in patients with cancer, (3) positive molecular assays for brucellosis such as PCR, (4) positive cultures of brucellosis that can be obtained from blood, peritoneal fluid, pleural fluid, bronchoalveolar lavage, cerebrospinal fluid and fluid taken from abscess collection, (5) granulomatous changes on histopathology, and (6) negative tumor markers [103,110,111,176].

Brucellar epidedymo-orchitis and testicular cancer

Epidedymo-orchitis (EO) is the commonest urological manifestation of brucellosis [178]. It occurs predominantly in young individuals and it presents with testicular swelling or mass, abscess formation, testicular atrophy and pain which may be absent [179-182]. The typical features of *Brucella*-related EO include: presence of an occupational risk factor, seasonal incidence, gradual onset, long duration of clinical manifestations, typical undulant fever, absence of severe leukocytosis, absence of lower urinary tract symptoms, relatively minimal signs of florid inflammation, unilateral involvement in most cases and relapses which are rarely encountered [178,183,184]. Mild to moderate leukocytosis is usually present and CRP is usually elevated [178]. Histology of the testis may reveal inflammatory changes, abscess formation, atrophy and fibrosis in addition to granulomatous changes [179,180,182].

Clinical data based on careful history and meticulous physical examination in addition to laboratory findings based on serological assays are usually sufficient to make the diagnosis of *Brucella*-related EO [183]. However, early detection and appropriate therapy of *Brucella*-related EO are essential and brucellosis should be considered as a possible cause of EO and testicular swellings [184]. Also, *Brucella*-related EO should be included in the differential diagnosis of testicular tumors in patients living in areas that are endemic for the disease [178-183] In patients with EO caused by brucellosis, conservative management in the form of combination of antibiotics is usually adequate [178,183,184]. Unfortunately, patients with *Brucella*-related EO may undergo unnecessary orchiectomy as the initial suspicion may be testicular carcinoma [179,180,182].

Brucellosis and rheumatic diseases

Infections in patients with rheumatic diseases cause significant morbidity and mortality [185]. Unfortunately, the diagnosis or recognition of infections in patients with rheumatic diseases may be difficult and delayed due to the following reasons: (1) the clinical manifestations of certain infections such as brucellosis may be indistinguishable from those of the underlying disease, and (2) the typical signs and symptoms of these infectious complications may be

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atypical or entirely absent [185]. Patients with rheumatic disorders are susceptible to infections with various micro-organisms, particularly bacteria and opportunistic agents due to the following factors: (1) the underlying rheumatic disorders, and (2) the administered immunosuppressive agents such as: corticosteroids, azathioprine, cyclophosphamide, anti-TNF therapy such as infliximab and targeted therapies such as rituximab [173,185-187].

TNF plays an important role in the host defense mechanisms and anti-TNF therapies may increase the risk of infections in patients with rheumatic diseases [173]. Brucellosis should be kept in mind, particularly in endemic areas, in patients receiving anti-TNF therapies as brucellosis has been reported in patients with RA receiving infliximab [173,186,187]. In patients with RA, infection is a major comorbidity and is related to the immunosuppressive therapies given and to the intrinsic effects of RA on certain body organs specifically the musculoskeletal system, while in patients with systemic lupus erythromatosis, infection is a cause of hospital admission and is a leading complication following admission [185].

Diagnosis of brucellosis

The laboratory tests that are used in the diagnosis of brucellosis include:

(1) Microbiological cultures: isolation of the organism from clinical samples such as blood, bone marrow, pus and tissues. Cultures give a low yield rate and identification of the organism and subsequent susceptibility testing take time, so treatment of brucellosis may be delayed [188].

(2) Serological tests: several serological techniques are used and these include: Coomb's test, slide or tube agglutination, enzyme-linked immunosorbent assay (ELISA), immunocapture agglutination, immunochromatographic lateral flow, *Brucella*-Capt, and indirect fluorescent antibody test as shown in Table 2, [63]. Serological tests are more useful but not internationally standardized [188]. Antibodies may remain elevated despite successful treatment, cross-reactions may occur and different cut-offs are needed for various levels of endemicity [188].

(3) Molecular assays: these include RT-PCR. Molecular tests may reduce the time to reach diagnosis, but diagnostic criteria for active infection have not been defined [188]. Each of the above tests has advantages and limitations. Therefore, interpretation of their results should be made carefully and in conjunction with the available clinical data [63].

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 [1,61,189,190]. However, none of these hematological abnormalities is specific or characteristic for brucellosis [190].

Thrombocytopenia is occasionally encountered and may be severe. Thrombocytopenic purpura has also been reported in patients

Table 2 : Serological Diagnosis of Brucellosis.	
Test	**Details**
Rose Bengal test	- Agglutination test based on reactivity of antibodies against smooth lipopolysaccharide (LPS). - High sensitivity and rare false positive results. - The present WHO guidelines recommend confirmation of this test by other assays such as serum agglutination test.
Coombs test	- Used for detection of incomplete, blocking and non-agglutinating immunoglobulin G (IgG). - It is time consuming and technically difficult as it requires skilled personnel. - It is not routinely performed in clinical laboratories. - However, it is the most suitable and sensitive test for confirmation of complicated, relapsing and chronic cases.
Fluorescence polarization test	- Valuable alternative to conventional serological tests. - Sensitivity: 96% for culture confirmed brucellosis. - Specificity: 98% .
ELISA test	- There are 3 available ELISA assays: (1) IgG, IgA and IgM antibody tests, (2) the standard tube agglutination test [SAT], and (3) 2-mercaptoethanol test [2-MET]. - SAT is the gold standard ELISA assay for the diagnosis of brucellosis particularly in endemic areas. - ELISA is an excellent method for: screening large populations for *Brucella* antibodies and differentiation between acute and chronic cases. - ELISA is the test of choice for complicated and chronic cases particularly when the diagnosis is highly suspected and other tests are negative.
Immunocapture agglutination test, *Brucella* Capt (BCAP)	- Can detect agglutinating and non-agglutinating antibodies with high sensitivity. - Easy to perform within 24 hours, but is expensive. - Based on the immunocapture-agglutination of the total anti-*Brucella* antibodies. - Can be used as a second level serological test in brucellosis.
Dipstick assay	- The IgM dipstick assay is one of the tests that have been adapted to detect IgM antibodies to small LPS. - The assay has high sensitivity for brucellosis lasting less than 3 months.
Lateral flow assay	- It is a simplified version of the ELISA test. - It detects *Brucella* IgM and IgG antibodies by an immunochromatographic method. - It is rapid, simple and easy to perform. - It uses a drop of blood obtained by a finger prick and can be performed at the bedside.
Rapid slide agglutination test	- It is a suitable screening test for the diagnosis of human brucellosis. - It can detect human infection with *B. canis*.
WHO: World Health Organization ELISA: Enzyme-linked immunosorbent assay.	

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 [191,192]. Hemolytic anemia that may be acute and Coomb's positive can also be seen [4,193-199]. Despite the severity of MAHA, complete recovery has been encountered with early and prompt therapy using plasma exchange, antimicrobial therapy for brucellosis and corticosteroids [200-203]. 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 [204].

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 [106,146] In patients having brucellosis and hematologic malignancy, simultaneous treatment of both the infection and the hematologic malignancy should be considered [61].

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, [61,189,205,206]. Brucellosis causes granulomas in the bone marrow and other tissues and these granulomas are usually small, non-caseating and they resemble sarcoid granulomas [46,61,189]. Histologically, they consist of epitheloid cells, polymorphonuclear leukocytes, lymphocytes and few giant cells as shown in Table 3, [46,205-208].

Brucella cultures

Brucella species can be cultured from blood, bone marrow, other tissues and body fluids such as liver, skin and pleural fluid [208-213].

Blood cultures in brucellosis

In patients with brucellosis, the range of blood culture positivity varies from 6% to 92% of patients depending on the following factors: (1) stage of the disease: acute, subacute or chronic, (2) the levels of *Brucella* titers, (3) the microbiological culture technique utilized and (4) prior antimicrobial therapy [23,208-210]. Isolation of these intracellular organisms from blood cultures is restricted by the slow growth of *Brucella* species and by the effect of previous antimicrobial

chemotherapy [208,209].

There are three main types of culturing techniques: (1) the traditional Ruiz-Castaneda method, (2) the automated culture systems and (3) the yield-optimizing methods including the lysis concentration technique [214,215]. Once a fastidious organism such as *Brucella* species is suspected, extension of the incubation period of blood cultures for days to weeks is usually needed to improve the yield rates of the traditional methods [214-216]. Additionally, the utilization of various automated culture systems has significantly decreased the period of time required to obtain a positive culture and has improved the yield rates [214,215].

Cultures of bone marrow and other body fluids

Bone marrow examination and *Brucella* cultures of the marrow aspirate are indicated under the following circumstances: (1) in patients strongly suspected to have brucellosis on clinical grounds but have negative serological tests, (2) in patients with FUO, particularly in geographic locations that are endemic for the disease, (3) in patients having unexplained articular or hematological involvement who live in endemic areas, and (4) in areas where advanced facilities such as automated culture systems or molecular techniques are not readily available [207,208,213,217].

Bone marrow culture for *Brucella* species may be positive more frequently than blood cultures and may be positive in the absence of positive *Brucella* serology or blood cultures. The yield of bone marrow cultures may reach 92% in patients who are strongly suspected to have brucellosis [210]. However, in a study that included 102 patients having brucellosis, the yield rates of blood cultures compared to bone marrow cultures were as follows: 66% versus 46% in acute brucellosis, 31% vs 21% in subacute infection and 0.0% vs 8.0% in chronic brucellosis, while the overall yield rates were 38% compared to 34% [210]. In addition to bone marrow cultures and in order to increase the yield of positive cultures, it is also recommended to try to culture aspirates or fluids obtained from: liver, lymph nodes, pleural space, bronchoalveolar lavage, joints and skin lesions in areas that lack advanced technology to diagnose brucellosis [214].

Serology in the diagnosis of brucellosis:

Several serological tests are available for the diagnosis of brucellosis [63,188]. However, they vary considerably regarding several aspects including: applications in various situations and usefulness as reflected their sensitivity and specificity as shown in Table 2, [49,63,188,217-230].

New biomarkers of brucellosis

Brucellosis may mimic rheumatoid arthritis clinically. Positive serological tests for rheumatic and autoimmune diseases such as rheumatoid factor (RF) and antinuclear antibody (ANA) are encountered in a relatively high proportion of patients with brucellosis [231]. Therefore, in endemic locations for brucellosis, interpretation of positive serology for rheumatic and autoimmune diseases such as RF and ANA should be taken into consideration. Discrimination between brucellosis and rheumatoid disorders,

Table 3: Differential diagnosis of brucellosis based on bone marrow (BM) histology.

BM granulomas	BM hemophagocytic lymphohistiocytosis
1- Bacterial infections: - *Mycobacterium tuberculosis* - Typhoid fever - Tularemia - Syphilis - Leprosy **2- Fungal infections:** - Histoplasmosis - Cryptococcosis - Coccidioidomycosis **3- Rickettsial infections:** - Q fever **4- Viral infections:** - *Cytomegalovirus* - *Epstein-Barr virus* - *Varicella-zoster virus* **5- Parasitic infections:** - Leishmaniasis - Toxoplasmosis	**1- Viral infections:** Epstein-Barr virus, *Cytomegalovirus*, *Herpes Simplex* *virus*, *Varicella-zoster virus*, *Human Immunodeficiency* *virus*, *Hepatitis virus*, *Adenovirus*, *Influenza virus*, *Parvovirus*, *Human Herpes viruses* types 6 and 8. **2- Other infections:** *Mycobacteria*, spirochetes, parasites and fungi. **3- Malignancy such as lymphoma.** **4- Macrophage activation syndrome associated with autoimmune diseases.**

both clinically and serologically, may be difficult in regions that are endemic for brucellosis [231].

In *Brucella* infections: (1) serum nitric oxide levels are modestly elevated, and (2) IL-6, IL-8 and IL-2R are usually elevated. The extent of elevation of these cytokines depends not only on the severity but also on the clinical pattern of the disease [232]. In patients with *Brucella* bacteremia or brucellosis with positive bloodstream infection, the following biomarkers of sepsis have been reported to be positive: (1) circulating micro-RNAs (miRs) such as miR-25, miR-133a, miR-146, miR-150, and miR-223; and (2) serum pro-calcitonin levels which can be used as surrogate markers to exclude bacteremia [233,234].

Molecular tests in the diagnosis of brucellosis

PCR is an in vitro technique for nucleic acid amplification which is commonly used to diagnose infectious diseases [235]. The direct culture and immunohistochemistry can be used for detecting infection with *Brucella* species, but PCR can potentially address the limitations of these procedures [235]. It can be used for pathogen detection, genotyping and quantification and it has the following advantages: high sensitivity and specificity, reproducibility and technical ease. Currently, PCR is one of the most useful assays for the diagnosis of human brucellosis [235]. PCR-based assays allow rapid and more sensitive identification of *Brucella* at species and biovar levels and their implementation into the clinical setting will likely improve therapeutic outcomes. Unfortunately, the current PCR protocols lack standardization [235,236].

PCR-based testing methods are faster and more sensitive than the traditional methods used in the diagnosis of brucellosis [236]. However, sensitivity, specificity and issues of quality control and quality assurance of the PCR assays vary between laboratories and unfortunately standardization of sample preparation, target genes and detection methods is still lacking [92,236-238]. Early diagnosis and pre-treatment prediction of clinical outcome will have a positive impact on the management of patients with brucellosis [92,236-238].

Combined with serological assays, PCR can be applied for the diagnosis of new cases of brucellosis, asymptomatic but highly exposed individuals in addition to relapsed cases regardless duration or type of the disease without relying entirely on blood cultures, particularly in chronic cases [92,239]. Combined PCR-ELISA technique is an immune-detection method that can directly quantify PCR product as it detects the nucleic acid rather than the protein [240]. It has much higher specificity and sensitivity than PCR alone. Additionally, it is easy to perform, yields results rather quickly and reduces the risk of contamination [240]. It has recently been introduced into the molecular diagnostic techniques of brucellosis and initial results of its use in acute human brucellosis are promising, so it may become a valuable tool to diagnose *Brucella* infections in immunocompromised hosts in particular [240,241].

Whole genome sequencing and MLVA

Whole genome sequencing of *B. canis* strain, BCB018, has been isolated from humans [242]. Also, whole genome sequencing of 10 diagnostic *Brucella*phages propagated on 2 *B. abortus* strains (141

and 519) has revealed: (1) fine scale patterns in the genetic structure of these phages, and (2) multiple common sequence variations across similar genes [243].

Multi-locus variable number tandem repeats (VNTR) assay (MLVA) has the ability to: (1) identify and discriminate between different *Brucella* species which display significant genetic diversity, (2) be utilized as an epidemiological tool, and (3) be used in brucellosis control and eradication programs [244,245]. The use of MLVA has 2 recent findings: (1) the isolation of *B. suis* from cattle, and (2) the genetic correlation between *B. abortus* isolates in humans and animals [244,245].

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 [247]. The most common infectious causes of FUO are: tuberculosis, endocarditis, typhoid fever, brucellosis, *CMV* infection and acquired immunodeficiency syndrome in western countries [248]. 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 [249].

PET scans in patients with PUO and brucellosis

Fluoro-18-fluoro-2-deoxy-D-glucose (FDG) accumulates in malignant tissues and at the sites of infection and inflammation [248]. Positron emission tomography (PET)/CAT scans are the procedures of choice for the diagnosis and follow up of certain malignancies particularly lymphomas. The currently available data in the literature indicate that FDG-PET scan is an important second-line procedure in the management of approximately 50% of patients with FUO and that its utilization in the diagnosis and follow up of several infections is on the rise [248].

In patients with spondylodiskitis due to brucellosis, PET/CAT scans can provide additional information on the spread of infection compared to magnetic resonance imaging. Successful treatment of brucellosis is associated with a significant decrease in the standard uptake value, thus PET/CAT scan may be a complementary method for determining the efficacy of treatment and the need for further antimicrobial chemotherapy [250]. In a patient having pulmonary nodules caused by *Brucella* infection, increased FDG uptake was encountered not only in the pulmonary lesions, but also in the hilar and mediastinal lymph nodes [251].

Treatment of brucellosis

The main treatment schedules of human brucellosis, obtained from several meta-analyses and few international recommendations, are shown in Table 4, [15,252-256]. Tigecycline is a new glycylcyclin compound which is more potent than tetracycline. Replacing

tetracycline by tigecycline may increase the efficacy of anti-*Brucella* treatment and decrease the duration of anti-*Brucella* therapy [257,258] Tigecycline has a promising future in the treatment of brucellosis and it may replace tetracycline which is still the mainstay of anti-*Brucella* treatment. Studies on tigecycline in geographic locations that are endemic for brucellosis have shown excellent in vitro activity and high antimicrobial susceptibility levels [257,258].

Lack of awareness among clinicians, low index of suspicion and non-availability of diagnostic tests can all lead to missed diagnosis of brucellosis [259]. The disease is easily treatable and can be completely cured but failure to diagnose brucellosis early may lead to delayed institution of appropriate antimicrobial therapy and this increases the chances of treatment failure [259]. Having a high index of suspicion, prompt diagnosis and appropriate as well as adequate treatment can cure the patient, prevent chronic morbidity and prevent loss of valuable time to treatment of the infection at an early stage [259]. It has been found that successful management of brucellosis can be

Table 4: Main Treatment Schedules for Human Brucellosis.

Reference	Solera (MA) 227	Skalsky (MA) 226	del Pozo (MA) 225	Yousefi-Nooraei (MA) 224	Alavi (MA) 223	WHO / FAO 1	Ioannina (IR) 15
Year of publication	1994	2008	2012	2012	2013	1986	2007
Studies/trials included	6	30	17	25	24	-	-
First Line Therapy	Streptomycin + Doxycycline	Doxycycline for 6 wks + Rifampicin for 6 wks OR Gentamicin for 2 wks	Doxycycline for 6 wks + Streptomycin for 2 wks OR Doxycycline for 6 wks + Gentamicin for 1 wk	Doxycycline for 6 wks + Streptomycin for 2-3 wks	Doxyxycline for 6 wks + Streptomycin for 2-3 wks	Doxycycline for 6 wks + Rifampicin for 6 wks	Doxycycline for 6 wks and Streptomycin for 2-3 wks
Alternative Therapy	-	Doxycycline for 6 wks + Gentamicin for 2 wks	Doxycycline + Rifampicin OR Ofloxacin + Rifampicin OR Doxycycline + Cotrimoxazole	Doxycycline + Rifampicin for 6 wks	Doxycycline + Rifampicin for 6 wks	Doxycycline for 6 wks + Streptomycin for 2-3 wks	Doxycycline for 6 wks + Rifampicin for 6 wks
Second Line Therapy	Rifampicin + Doxycycline	Doxycycline for 6 wks + Streptomycin for 2 wks	-	Quinolone + Rifampicin for 6 weeks	Quinolone-based therapy + Doxyxycline OR Rifampicin	-	Doxycycline for 6 wks + Gentamicin for 1 wk
Optional Therapy	-	Cotrimoxazole + Doxycycline for 6 wks OR Cotrimoxazole + Rifampicin for 6 weeks	Monotherapy in patients with low risk of relapse	-	Doxycycline + Cotrimoxazole for 6 wks	Cotrimoxazole	Cotrimoxazole for 6 wks OR Ofloxacin for 6 wks OR Ciprofloxacin for 6 wks
Not Recommended	-	• Monotherapy • Treatment for less than 30 days • Quinolone-based therapy	Triple therapy	Rifampicin in areas that are endemic for tuberculosis	• Monotherapy • Short-term treatment	-	Azithromycin OR Meropenem

MA: meta-analysis
WHO: World Health Organization
wks: weeks
IR: international recommendation
FAO: Food and Agriculture Organization

reflected by a decrease in oxidative stress. Hence, it is possible that oxidant and anti-oxidant parameters could be used to monitor the response to treatment in patients with brucellosis [260].

Drug resistance and antibiotic susceptibility

In order to decrease the development of drug resistance and the incidence of complications of brucellosis, it is important to have antimicrobial therapy guided by antibiotic susceptibility testing [261]. However, antimicrobial susceptibility of *Brucella* species varies considerably from one place to another [257,258,262-265]. In two studies performed in Turkey 10 and 11 years ago, *Brucella* species was showing excellent susceptibility to tetracycline, rifampicin, ciprofloxacin and azithromycin but some resistance to ceftriaxone [263,264]. In a recent Brazilian study, *Brucella* species was found to be susceptible to doxycycline, streptomycin and gentamicin but high degree of resistance to rifampicin and TMP/SMZ [262]. Also, in a recent Malaysian study, high level of resistance of *Brucella* species to rifampicin was found [265]. As only 38% of *Brucella* strains are susceptible to co-trimoxazole, it is usually recommended to administer TMP/SMZ in combination with tetracycline or streptomycin [261].

Fluoroquinolones exhibit broad spectrum antibacterial activity and hence they are attractive candidates for use against infections caused by intracellular bacteria such as *Brucella* species due to their oral bioavailability, high tissue concentrations, evidence of intracellular penetration and in vitro activity against *Brucella* species [266]. Ciprofloxacin had a good promise initially, but its use as a sole agent in first line therapy has been excluded because of the following reasons: the lack of bactericidal activity against *Brucella* species, the development of drug resistance during therapy and the high relapse rates encountered [266]. The new generations of fluoroquinolones such as moxifloxacin, gatifloxacin, ofloxacin, grepafloxacin, trovafloxacin and sitafloxacin have shown excellent in vitro activities against *B. melitensis* [266]. Rifampicin is a potent broad-spectrum antibiotic and is an integral component of the combination therapy used in the treatment of human brucellosis, but it should be used with extreme caution in areas that are endemic for tuberculosis [267].

Treatment considerations in immunocompromised patients

Once the treatment of brucellosis in an immunocompromised patient is decided, the following points should be taken into consideration: (1) the same antimicrobials and therapeutic schedules can be used, but the duration of treatment may be longer, (2) interactions between antimicrobials used to treat brucellosis and cytotoxic chemotherapy or immunosuppressive therapies given to control the underlying disease should be avoided if possible, (3) in uncomplicated cases of brucellosis, simultaneous administration of antimicrobials and immunosuppressive or cytotoxic therapy may be justified, and (4) in patients having *Brucella* bacteremia or complicated *Brucella* infections, at least 2 weeks of antimicrobial therapy should be administered before subjecting the patient to cytotoxic chemotherapy or immunosuppressive treatment [95,99,107,109,114,117-119,253].

Control of brucellosis

The main components of brucellosis control and eradication strategies are: (1) elimination of the pathogen at its animal source by hygiene measures such as careful herd management and health education, (2) improving quality of the veterinary services and establishment of diagnostic laboratories that adopt international standards, (3) adoption of appropriate control and eradication programs, (4) active and continuous surveillance and identification of animals and herds at high risk, (5) vaccination of young female animals while the live-attenuated animal vaccines are contraindicated in immunocompromised humans, (6) testing and slaughtering of seropositive adult animals, (7) health education and application of strict hygiene measures to personnel in direct contact with animals, (8) coordination and cooperation between public health officials, veterinary officers and various governmental sectors such as expanded governmental, regional and international health organizations, (9) animal control with restriction of animal transportation across open borders, (10) pasteurization of milk, prompt diagnosis and appropriate treatment of infected humans, and (11) maintaining a high index of suspicion for the infection in endemic areas is of vital importance [20,99,100,117,268-270].

Conclusions and Future Directions

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 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.

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