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Article

Brucellosis in Patients Infected with the Human Immunodeficiency Virus

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Abstract Brucellosis has been described rarely in patients infected with HIV, despite the fact that eradication of intracellular brucellae is largely dependent on cell-mediated immunity. The characteristics of all patients with HIV infection and brucellosis seen in seven Spanish hospitals are reported. Since the beginning of the AIDS epidemic, 12 HIV-infected patients were diagnosed with brucellosis (8 with cultures positive for *Brucella* spp., 4 with high anti-*Brucella* antibody titers). Most patients were male and intravenous drug users. Eleven patients had no symptoms of HIV infection when first diagnosed with brucellosis and had relatively preserved cellular immunity (median CD4+ cell count 588, range 136–1006). There was a clear epidemiologic antecedent for acquisition of brucellosis in 11 patients. Clinical symptoms included fever, arthromyalgia, and sweating in all patients; four patients presented with focal disease. All patients had high agglutinin titers, and eight of nine had cultures positive for *Brucella*. Therapy with doxycycline and streptomycin was curative in all cases. Two patients experienced a recurrence of symptoms after initial treatment, although no microbiological relapses were documented after a median follow-up period of 18 months. HIV infection does not seem to increase the incidence of brucellosis. Since most cases occur in asymptomatic patients with relatively preserved immunity, the epidemiology, clinical presentation, diagnosis, response to therapy, and outcome are similar to those observed in non-HIV infected patients.

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Introduction

Brucellosis is a worldwide zoonotic disease with an especially high prevalence in certain geographical areas, including the Mediterranean basin, the Arabian Gulf, the Indian subcontinent, and parts of Mexico and Central and South America. While programs to control and eradicate the disease in domestic animals have resulted in a dramatic decline in the incidence of human brucellosis in some countries, it still persists as an important health problem in others [1–7]. Human brucellosis usually affects non-compromised hosts, with a few cases having been described in non-HIV-infected, immunosuppressed patients [8, 9].

Infection with the human immunodeficiency virus (HIV) causes profound abnormalities in humoral and cellular immune responses. Since eradication of intracellular brucellae is largely dependent on cell-mediated immunity, a frequent association between HIV infection and brucellosis in areas where the two diseases are prevalent could have been anticipated. Surprisingly, after 15 years of the AIDS epidemic, only a few cases of brucellosis in HIV-infected patients have been reported, and the relationship between the two infections remains to be investigated [10–13].

Spain has a high prevalence both of brucellosis, caused mainly by *Brucella melitensis*, and of HIV infection; the infections are coincident in some areas [14, 15]. This has given us the opportunity to explore the interaction between the two infections. We report herein the characteristics of 12 patients with HIV infection and brucellosis and review five cases reported previously in the medical literature.

Patients and Methods

A survey of cases of brucellosis in HIV-infected patients was conducted in 23 Spanish hospitals. We included hospitals that attend large populations of HIV-infected patients and/or are located in areas where brucellosis is endemic. The registries of HIV-infected patients and discharge diagnoses in these hospitals were reviewed in order to find HIV-infected patients who had been diagnosed with brucellosis.

For purposes of this report, we reviewed the clinical charts of all patients coinfected with HIV and *Brucella* attended at these hospitals since 1981. Only seven hospitals reported eligible cases for the study during the period from 1981 through 1995.

Infection with HIV was diagnosed in all cases by an enzyme immunoassay and confirmed with Western blot. The diagnosis of brucellosis required either the isolation of brucellae from blood or other fluid/tissue, or the demonstration of high (>160) or rising titers of antibodies to *Brucella* smooth lipopolysaccharide in the serum. Standard procedures were used for serological testing [rose bengal, tube agglutination test (TAT), anti-*Brucella* Coombs test] as well as for culture and identification of *Brucella* spp. in all the centers [16–19].

Results

Twelve HIV-infected patients in seven Spanish hospitals were diagnosed with brucellosis during the period of study. Their main epidemiological and clinical features are described in Table 1. Eleven patients were male, and the median age was 28 years (range 22 to 34). Risk factors for HIV infection included intravenous drug abuse in nine patients and unprotected sex in three (2 heterosexual, 1 homosexual). Only one patient had been diagnosed with AIDS, manifested by esophageal candidiasis. The other 11 patients had not experienced any HIV-related symptom or complication prior to the diagnosis of brucellosis. HIV infection was diagnosed after brucellosis in nine of these 11 patients. Only one patient was receiving antiretroviral therapy.

A presumed source of the brucellosis infections was identified in 11 patients, including ingestion of unpasteurized milk or milk products in six patients and direct contact with infected animals (sheep and/or goats) in five patients. This was the first episode of brucellosis in all patients.

Most patients described a gradual onset of the disease. Time of evolution of symptoms until the patients came to the hospital ranged from 2 weeks to 3 months. Fever, sweats, myalgia, and arthralgia were common to most patients. Other symptoms at presentation included dry cough (2 patients), headache (2 patients), weight loss (2 patients), and abdominal pain (1 patient).

Physical examination revealed liver and/or spleen enlargement in nine of the 12 patients. Four patients presented with signs of focal disease: one with acute bilateral epididymoorchitis, two with osteoarticular involvement (knee arthritis and sacroiliitis, in 1 patient each), and one with a subcutaneous abscess in the left thigh.

Blood and biochemical analysis results were unremarkable. The median leukocyte count was 5000/mm^3 (range 2700–11100), the median hemoglobin level 14.4 g/dl (range 9.8–15.8), and the median platelet count 146000/mm^3 (range 51000–342000). Three patients had leukopenia (<4000 leukocytes/mm^3), two had anemia (hemoglobin <10 g/dl), and two had thrombocytopenia (<100000 platelets/mm^3). The only remarkable serum biochemical abnormality was a mild elevation of liver enzymes in four patients. CD4+ cell counts were determined in nine patients at the time brucellosis was diagnosed. The median CD4+ cell count was 588/mm^3 (range 136–1006), with only one patient having <200 CD4+ cells/mm^3.

The initial sera from all 12 patients gave positive results in the rose bengal test and significant TAT titers. Agglutinin titers ranged from 1:160 to 1:10240. No

patient converted from a negative to a positive titer. Anti-*Brucella* Coombs test was positive in the five patients in whom the test was performed. Blood cultures for *Brucella* were requested for eight patients; seven of these had positive blood cultures, including one patient who also had a positive culture of a soft tissue mass aspirate. In addition, one patient had *Brucella* spp. isolated from synovial fluid.

All patients received adequate treatment soon after the diagnosis of brucellosis. Eleven patients received doxycycline (100 mg b.i.d. orally for 6 weeks) plus streptomycin (1 g/day i.m. for 2 weeks), and one patient received doxycycline plus gentamicin (80 mg t.i.d. i.v. for 1 week). All patients responded well to the antibiotics administered. Defervescence occurred within the first week of therapy in eight of the nine patients in whom it could be adequately assessed. The four patients with localized disease experienced improvement of their focal signs in 1 to 2 weeks.

During therapy and after its completion, blood cultures and serological tests for *Brucella* were performed in all the patients at varying intervals. No patient had a microbiological relapse; blood cultures were persistently negative. The patient who presented with knee arthritis had a clinical relapse with orchitis, negative blood cultures, and a persistent agglutinin titer of 1:1280. Therapy with doxycycline plus gentamicin was curative, with no further relapse occurring. Another patient (case 12) had a clinical relapse manifested by an increase in TAT titers of up to 1:2560. The patient, who was a shepherd, was in continuous contact with infected animals.

The evolution of HIV infection could be observed during a median follow-up period of 18.5 months (range 2 months-9 years). Four patients were lost to follow-up at 2, 8, 12, and 14 months, respectively. Of the remaining eight patients, two developed AIDS, manifested by extrapulmonary tuberculosis, 9 months and 3 years after the diagnosis of brucellosis, respectively (cases 9 and 11). The three patients with AIDS died during the follow-up period, at 13, 47, and 69 months, respectively. Five patients remain asymptomatic, although two of them have begun antiretroviral therapy for a decline in their CD4+ cell counts.

Discussion

We found a low rate of brucellosis in HIV-infected patients. In addition, the epidemiology, clinical characteristics, diagnosis, response to therapy, and outcome of the disease are similar to those observed in non-HIV infected patients, a finding that is possibly related to the fact that most cases occurred in asymptomatic patients with relatively preserved cellular immunity. Brucellosis is classically a disease of the immunocompetent host. This is evident by the scarce number of cases of the disease in immunocompromised subjects reported to date [8, 9]. In a recent study of 530 patients with brucellosis, neither HIV infection nor other immunosuppressive diseases were mentioned among the predisposing conditions [20]. Although both humoral and cellular immunity play a role in the host response against brucellae [21], no single immunologic defect has been described as clearly predisposing to infection or disease with the organism.

Infection with HIV causes a profound impairment of B and T cell immune responses that predisposes to infections with opportunistic organisms, including multiple intracellular pathogens [22]. For this reason, it seemed reasonable to expect, at the beginning of the AIDS epidemic, that HIV-infected patients would be more vulnerable to brucellosis. The low number of HIV-infected subjects with brucellosis in Spain, where prevalence of the disease is still high in some areas, clearly argues against this hypothesis. HIV-infected patients with brucellosis could be found in only seven hospitals among 23 surveyed centers where brucellosis and HIV infection have been frequently diagnosed during the last 15 years. Furthermore, a recent article from Spain reported only 22 cases of brucellosis among 17592 infectious complications in intravenous drug users during a 14-year period [23]. In addition to the 12 patients presented here, only five additional cases have been described in detail in the literature, all from Spain [10–13] (Table 2).

Reasons for the relatively low incidence of brucellosis in HIV-infected patients are not clear. Whether it is the consequence of resistance to infection with the organism or the lack of progression from infection to disease is largely unknown. It could be argued that the epidemiology of brucellosis and HIV infection may not be entirely coincident. Countries where brucellosis is common may have a low prevalence of HIV infection [24]. Within a country, brucellosis is most often diagnosed in rural areas, while HIV infection is more frequent in urban areas. Thus, the low incidence of brucellosis could be a consequence of little exposure to the organism. A recent report from Nairobi, however, provides some evidence against this argument [25]. Serological evidence of exposure to *Brucella* was found in more than one-third of HIV-infected and HIV-uninfected individuals who had never developed clinical manifestations of the disease. It seems, then, that HIV-infected patients who are exposed to the brucellae become infected with the organism, yet most of them do not develop overt clinical disease. It is still unknown whether the incidence of the disease, as well as its clinical course, would be different among more severely immunocompromised patients. Most of our patients and those reported previously in the literature had a relatively preserved cellular immunity.

Table 1 Brucellosis in HIV-infected patients

Patient no.	Age/sex	Risk factor for HIV	Stage of HIV disease	CD4+ cells/mm^3	Epidemiologic antecedent for brucellosis	Symptoms and signs	Focal disease
1	33/M	unprotected homosexual sex	asymptomatic	916	ingestion of unpasteurized milk	fever, sweats, arthralgia, myalgia	none
2	34/M	IVDA	asymptomatic	240	ingestion of unpasteurized milk	fever, pain over the left buttock, knee arthritis	sacroiliitis, knee arthritis
3	34/M	IVDA	AIDS	136	ingestion of unpasteurized milk	fever, arthralgia, splenomegaly	none
4	26/F	unprotected heterosexual sex	asymptomatic	ND	ingestion of unpasteurized milk	fever, sweats, arthralgia, splenomegaly	none
5	25/M	IVDA	asymptomatic	672	ingestion of unpasteurized milk	fever, sweats, weight loss, hepatosplenomegaly	orchitis
6	22/M	IVDA	asymptomatic	1003	contact with infected animals	fever, sweats, myalgia, hepatosplenomegaly	none
7	38/M	unprotected heterosexual sex	asymptomatic	ND	contact with infected animals	fever, malaise, arthromyalgia, hepatosplenomegaly	none
8	33/M	IVDA	asymptomatic	588	contact with infected animals	fever, sweats, arthralgia, splenomegaly	knee arthritis
9	26/M	IVDA	asymptomatic	ND	contact with infected animals	fever, arthraliga, myalgia, sweats, hepatosplenomegaly	none
10	24/M	IVDA	asymptomatic	900	ingestion of unpasteurized milk	fever, sweats, weight loss, hepatosplenomegaly	subcutaneous abscess
11	26/M	IVDA	asymptomatic	336	unknown	fever, hepatomegaly	none
12	21/M	IVDA	asymptomatic	314	contact with infected animals	fever	none

D, doxycycline; G, gentamicin; IVDA, intravenous drug abuser; ND, not done; S, streptomycin

[a] Recovered from synovial fluid

[b] Recovered from blood and subcutaneous abscess

Table 2 Characteristics of brucellosis in HIV-infected patients reported in the literature

Reference no.	Age/sex	Risk factor for HIV	Stage of HIV disease	CD4+ cells/mm^3	Epidemiologic antecedent for brucellosis	Symptoms and signs	Focal disease
10	34/M	IVDA	asymptomatic	570	resident in an endemic area	fever, headache, cough, rash	none
11	35/M	IVDA	asymptomatic	172	ingestion of unpasteurized milk	fever, abdominal pain, hepatosplenomegaly	none
11	30/F	IVDA	asymptomatic	150	none	fever, hepatosplenomegaly	none
12	23/M	IVDA	asymptomatic	406	not stated	fever, sweats, arthromyalgia, headache, cough, hepatosplenomegaly, papilledema	meningitis
13	37/M	IVDU	asymptomatic	476	previous brucellosis	fever, hepatosplenomegaly	none

D, doxycycline; IVDA, intravenous drug abuser; R, rifampin; S, streptomycin; wks, weeks

Agglutinins	Coombs test titer	Results of culture	Therapy	Response to therapy	Duration of follow-up (months)	Outcome
1:320	ND	negative	D+S	cure, no relapse	30	survival: asymptomatic, no antiretroviral therapy
1:160	1:160	ND	D+S	cure, no relapse	12	lost to follow-up
1:160	1:320	ND	D+S	cure, no relapse	13	death (*Rhodococcus equi* pneumonia)
1:320	ND	*Brucella* sp.	D+S	cure, no relapse	108	survival: asymptomatic, on antiretroviral therapy, (last CD4+ cell count 210/mm^3)
1:640	1:5120	*B. melitensis*	D+S	cure, no relapse	48	survival: asymptomatic, on antiretroviral therapy (last CD4+ cell count 378/mm^3)
1:640	1:640	*B. melitensis*	D+S	cure, no relapse	14	survival: asymptomatic, no antiretroviral therapy
1:160	ND	*B. melitensis*	D+S	cure, no relapse	2	lost to follow-up
1:10240	ND	*Brucella* sp.[a]	D+G	cure, relapse (orchitis)	8	lost to follow-up (last CD4+ cell count 353/mm^3)
1:1280	1:5120	*B. melitensis*	D+S	cure, no relapse	69	death (cryptococcal meningitis)
1:320	ND	*B. melitensis*[b]	D+S	cure, no relapse	14	lost to follow-up (last CD4+ cell count 580/mm^3)
1:320	ND	ND	D+S	cure, no relapse	47	death (disseminated tuberculosis)
1:320	ND	*B. melitensis*	D+S	cure, relapse (fever)	23	survival (last CD4+ cell count 329/mm^3)

Agglutinins	Coombs test titer	Results of culture	Therapy	Response to therapy	Follow-up in months	Outcome
1:160	1:640	*Brucella* sp.	D+R	cure, 2 relapses (positive blood cultures)	13	survival (last CD4+ cell count 228/mm^3)
1:220	1:1280	not stated	D+R	cure, no relapse	6	alive (last CD4+ cell count 420/mm^3)
1:40	1:1280	*Brucella* sp.	D+R	cure	3 wks	lost to follow-up
1:5120	1:5120	*B. abortus*	D+R	cure, no relapse	2	death (heroin overdose)
(−)	(−)	*B. melitensis*	D+R	cure, no relapse	36	survival, asymptomatic (last CD4+ cell count 1039/mm^3)

Opsonization and phagocytosis by polymorphonuclear leukocytes are considered the first line of defense against *Brucella* spp. Organisms that are not killed by polymorphonuclear leukocytes are ingested and killed by macrophages of the reticuloendothelial system, although some can survive and proliferate intracellularly. HIV-infected patients retain the activity of granulocytes and non-immune macrophages relatively intact in the course of their disease. This could explain the lack of progression from *Brucella* infection to disease in most patients, similar to what happens in the immunocompetent host.

Most HIV-infected patients who were diagnosed with brucellosis in this and other reports had a relatively preserved cellular immunity and were asymptomatic with respect to their HIV infection. Eleven of the 12 patients in our study were diagnosed with HIV infection after the diagnosis of brucellosis. The fact that brucellosis occurs early in the course of HIV infection favors the hypothesis that the association of the two diseases is entirely coincidental and clearly independent of the HIV-associated immune impairment. An epidemiologic antecedent suggestive of exposure to brucellosis could be documented in all of our patients. This stresses the importance of considering the diagnosis and of obtaining a detailed history in HIV-infected patients who live in or have traveled to areas where brucellosis is endemic or frequent.

The clinical presentation of brucellosis in these HIV-infected individuals with relatively preserved immune function is similar to that seen in immunocompetent patients. As in classical descriptions of brucellosis [26], the combination of fevers, sweats, arthralgia, myalgia, and liver and/or spleen enlargement was present in most of our patients and in most of those reported previously. Localized disease does not seem to occur more frequently among HIV-infected patients. Symptoms related to a single organ dominate the clinical presentation in up to 40% of HIV-negative patients with brucellosis, with bone/joint involvement being the most frequent complication [20, 27, 28]. Four of our patients presented with focal disease. One additional patient reported in the literature developed *Brucella abortus* meningitis [12]. Recently, a severely immunosuppressed AIDS patient who developed *Brucella melitensis* osteitis following craniotomy was described [29]. No patient presented with or developed more rare complications, such as gastrointestinal, pulmonary, or cardiovascular complications.

The approach to the diagnosis of brucellosis in HIV-infected patients is similar to that used in immunocompetent subjects. Except for one patient, *Brucella* grew in all cases when blood cultures were requested and maintained for a sufficient period of time. Serological diagnosis is also useful in HIV-infected patients. The rose bengal test (a card test that allows rapid detection of anti-*Brucella* agglutinins) was positive in all cases, as were TAT titers. We did not observe seroconversion among our patients, possibly due to the insidious course of the disease and the delay by the patients to seek medical attention. One of the patients described in the literature is an exception to this general rule [13]. The patient, who had blood cultures positive for *Brucella melitensis*, had persistently negative serological determinations, including TAT titers, anti-*Brucella* Coombs test, and indirect immunofluorescence.

The therapy of brucellosis is an important issue. Adequate treatment of brucellosis has been and remains a matter of controversy in some aspects. Although tetracycline compounds are accepted as the most effective antibiotics against *Brucella* infections, the choice of a second drug is not so clear. Both streptomycin and rifampin have been shown to be efficacious [30–36]. Although some reports have demonstrated large differences in efficacy favoring the use of streptomycin [32, 35, 36], other well-designed studies have shown similar results with the two drugs [30, 31]. The lower toxicity of rifampin and the advantages of oral administration of this drug as opposed to the parenteral administration of aminoglycosides led the World Health Organization to recommend the use of a combination of doxycycline/rifampin [37].

Adequate information about therapy and outcome of brucellosis was available for all of our patients and for those reported previously. Our 12 patients received a combination of doxycycline and an aminoglycoside (streptomycin in 11 cases, gentamicin in 1 case), while the five patients reported in the literature were treated with doxycycline and rifampin. The two regimens were associated with good tolerance and a good initial clinical response, even in patients with meningitis and other focal diseases. Our patients became asymptomatic within the first week of therapy, except for signs and symptoms of arthritis that may require up to 2 weeks to disappear. Thus, as shown by this limited experience, it seems that rifampin and streptomycin can be used with similar good efficacy and safety in the treatment of brucellosis in HIV-infected patients.

Most studies have shown that, with good compliance, therapy of brucellosis is associated with a relapse rate of less than 5% [31]. Relapses have also been infrequent in the HIV-infected population. One patient with peripheral arthritis who was treated with doxycycline for 6 weeks and with gentamicin for only 7 days had a recurrence of clinical symptoms that required one additional course of therapy. Therapy with doxycycline plus 2 weeks of gentamicin was curative, with no further relapse occurring. Repeated blood cultures were negative in all of our patients, and TAT titers became negative during the follow-up period. The low rate of relapses is especially intriguing since brucellae, like mycobacteria, salmonellae, and listeriae, are intracel-

lular organisms, and cell-mediated immunity is considered necessary for their eradication. Martín et al. [10] described a patient who had two relapses, documented by repeated blood cultures positive for *Brucella melitensis*, even in the absence of symptoms and despite adequate therapy for the infection. As an additional peculiarity of this case, TAT titers and anti-*Brucella* Coombs test became negative when relapses occurred. As previously mentioned, it cannot be established with the available data whether the clinical course of brucellosis and the relapse rate after therapy would be different, should the diseases develop in patients with more advanced HIV infection.

The evolution of HIV disease could be observed in some of our patients. It has been said that brucellosis is associated with a certain degree of immunosuppression [38]. Some studies have reported immunologic defects associated with the disease, including an inhibition of serum bactericidal activity, a decreased response to mitogens of spleen lymphocytes, a transient decrease in CD4+ cell count, an impaired activity of natural killer cells, and a decreased functional activity of T-lymphocytes [39–44]. It could then be expected that brucellosis accelerates the course of HIV infection. Our patients, however, have remained asymptomatic and immunologically stable for long periods after their recovery from brucellosis. Although the number of patients is small and no comparisons have been made with patients without brucellosis, the evolution of HIV infection in our patients seems not to have been influenced by the disease.

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References

1. Ariza J: Brucelosis, algunos aspectos de su epidemiologia. Enfermedades Infecciosas y Microbiologia Clínica (1989) 7:517–518
2. Buchanan TM, Hendricka S, Paton CH, Feldman RA: Brucellosis in the United States, 1960–1972. An abattoir-associated disease. Part III. Epidemiology and evidence for acquired immunity. Medicine (1974) 53:427–438
3. Lulu AR, Araj GF, Khateeb MI, Mustafa MY, Yusuf AR, Fenech FF: Human brucellosis in Kuwait: a prospective study of 400 cases. Quarterly Journal of Medicine (1988) 66:39–54
4. Mousa ARM, Elhag KM, Khogali M, Marafie AA: The nature of human brucellosis in Kuwait: study of 379 cases. Reviews of Infectious Diseases (1988) 10:211–217
5. Spink WW: The nature of brucellosis. University of Minnesota Press, Minneapolis, 1956, pp. 145–190
6. Wise RI: Brucellosis in the United States. Past, present and future. Journal of the American Medical Association (1980) 244:2318–2322
7. Young EJ: An overview of human brucellosis. Clinical Infectious Diseases (1995) 21:283–290
8. Oksenhendler E, Morinière B, Rouveix E: Brucellosis in hairy cell leukaemia. Transactions of the Royal Society of Tropical Medicine and Hygiene (1988) 82:336
9. Raziuddin S, Bilal N, Benjamin B: Transient T-cell abnormality in a selective IgM-immunodeficient patient with *Brucella* infection. Clinical Immunology and Immunopathology (1988) 46:360–367
10. Martín I, Ramos C, Gutiérrez A, Arazo P, Aguirre JM: Infección por VIH y brucelosis crónica. Enfermedades Infecciosas y Microbiologia Clínica (1992) 10:566–567
11. Pedro-Botet J, Coll J, Auguet T, Rubiés-Prat J: Brucellosis and HIV infection: a casual association? AIDS (1992) 6:1039–1040
12. Rubio A, Portu J, Zubizarreta J, Ayensa C: Meningitis por *Brucella abortus* en un paciente con infección por el virus de la immunodeficiencia humana. Medicina Clinica (Barcelona) (1992) 99:678
13. Valladares M, Viciana P, Martín A, del Nozal M: Brucelosis aguda e infección por VIH: una nueva particularidad. Enfermedades Infecciosas y Microbiologia Clínica (1993) 11:511–512
14. Ministerio de Sanidad y Consumo, Dirección General de Salud Pública: Comentario epidemiológico de las enfermedades de declaración obligatoria nacional. Año 1988. Boletin Epidemiológico Semanal (1989), No. 1825
15. Ministerio de Sanidad y Consumo: Epidemiologia del SIDA en España. DIN Impresores, Madrid, December (1995):7–90
16. Alton GG, Jones LM, Pietz DE: Laboratory techniques in brucellosis. World Health Organization Monograph No. 55 (1975), p. 11–67
17. Jones LM, Wundt W: International Committee on Nomenclature of Bacteria. Subcommittee on the Taxonomy of *Brucella*. Minutes of meeting. International Journal of Systematic Bacteriology (1971) 21:126–128
18. Morgan WP, Mackinnon DJ, Lawson JR, Cullen GA: The rose Bengal plate agglutination test in the diagnosis of brucellosis. Veterinaire Recherche (1969) 85:636–641
19. Ruiz-Castañeda M: Laboratory diagnosis of brucellosis in man. Bulletin of the World Health Organization (1961) 24:73–84
20. Colmenero JD, Reguera JM, Martos F, Sánchez de Mora D, Delgado M, Causse M: Complications associated with *Brucella melitensis* infection: Study of 530 cases. Medicine (1996) 75:195–211
21. Sulitzeanu D: Mechanisms of immunity against *Brucella*. Nature (1965) 205:1086–1088
22. Pantaleo G, Graziosi C, Fauci AS: New concepts in the immunopathogenesis of human immunodeficiency virus infection. New England Journal of Medicine (1993) 328:327–335
23. Grupo de Trabajo para el Estudio de Infecciones en Drogadictos: Estudio multicéntrico de las complicaciones infecciosas en adictos a drogas por vía parenteral en España: análisis final de 17.592 casos (1977–1991). Enfermedades Infecciosas y Microbiologia Clinica (1995) 13:532–539
24. Giasuddin ASM, Ziu MM, Shaafie IA: Brucella and HIV-1 antibodies in Libyan blood donors. Journal of Infection (1991) 22:294–296
25. Paul J, Gilks C, Batchelor B, Ojoo J, Amir M, Selkon JB: Serological response to brucellosis in HIV-seropositive patients. Transactions of the Royal Society of Tropical Medicine and Hygiene (1995) 89:228–230
26. Buchanan TM, Hendricka S, Paton CH, Feldman RA: Brucellosis in the United States, 1960–1972. An abbattoir-associated disease. Part III. Epidemiology and evidence for acquired immunity. Medicine (1974) 53:427–438
27. Ariza J, Pujol M, Valverde J, Nolla JM, Rufí G, Fernández-Viladrich P: Brucellar sacroiliitis: findings in 63 episodes and current relevance. Clinical Infectious Diseases (1993) 16:761–765
28. Mousa ARM, Muhtaseb SA, Almudallal DS, Khodeir SM, Marafie AA: Osteoarticular complication of brucellosis: a study of 169 cases. Reviews of Infectious Diseases (1987) 9:531–543

29. Galle C, Struelens M, Liesnard C, Godfraid J, Yaes N, Dewitte O, Farber CM, Clevenberg P, Van Vooren JP: *Brucella melitensis* osteitis following craniotomy in a patient with AIDS. Clinical Infectious Diseases 1997, 24:1012
30. Acocella G, Bertrand A, Beytout J, Durrande JB, García-Rodríguez JA, Kosmidis J: Comparison of three different regimens in the treatment of acute brucellosis: a multicenter multinational study. Journal of Antimicrobial Chemotherapy (1989) 23:433–439
31. Ariza J, Gudiol F, Pallarés R, Fernández-Viladrich P, Rufí G, Corredoira J: Treatment of human brucellosis with doxycycline plus rifampin or doxycycline plus streptomycin. A randomized, double-blind study. Annals of Internal Medicine (1992) 117:25–30
32. Ariza J, Gudiol F, Pallarés R, Rufí G, Fernández-Viladrich P: Comparative trial of rifampin-doxycycline versus tetracycline-streptomycin in the therapy of human brucellosis. Antimicrobial Agents and Chemotherapy (1985) 28:548–551
33. Cisneros JM, Viciana P, Colmenero J, Pachón J, Martínez C, Alarcón A: Multicenter prospective study of treatment of *Brucella melitensis* brucellosis with doxycycline for 6 weeks plus streptomycin for 2 weeks. Antimicrobial Agents and Chemotherapy (1990) 34:881–883
34. Colmenero JD, Hernández S, Reguera JM, Cabrera F, Rius F, Alonso A: Comparative trial of doxycycline plus streptomycin versus dosycycline plus rifampin for the therapy of human brucellosis. Chemotherapy (1989) 35:146–152
35. Solera J, Medrano F, Rodríguez M, Geijo P, Paulino J: Ensayo terapéutico comparativo y multicéntrico de rifampicina y doxiciclina frente a estreptomicina y doxiciclina en la brucelosis humana. Medicina Clinica (1991) 96:649–653
36. Solera J, Rodríguez Zapata M, Geijo P, Largo J, Paulino J, Saez L: Doxycycline-rifampin versus doxycycline-streptomycin in treatment of human brucellosis due to *Brucella melitensis*. Antimicrobial Agents and Chemotherapy (1995) 39:2061–2067
37. Food and Agriculture Organization-World Health Organization: FAO-WHO Expert Committee on Brucellosis (6th report). WHO Technical Report Series (1986) 740:56–57
38. Burgaleta C: Actividad funcional de las células fagocíticas en la brucelosis. In: Baquero F, Buzón L (eds): Proceedings of an international symposium on brucellosis. Garsi, Madrid (1985), p. 43–49
39. Gazapo E, González Lahoz J, Subiza JL, Baquero M, Figueredo MA, Gómez de la Concha E: Subpoblaciones linfocitarias en la evolución de la brucelosis. Revista Clinica Española (1990) 186:369–373
40. Renoux M, Renoux G: Brucellosis immunodepression and levamisole. Lancet (1977) i: 372
41. Riglar C, Cheers CH: Macrophage activation during experimental murine brucellosis. Inhibition of in vitro lymphocyte proliferation by *Brucella* activated macrophages. Cell Immunology (1980) 49:168–177
42. Rodríguez-Zapata M, Alvarez Mon M, Salmerón I, Prieto A, Manzano L, Salmerón OJ: Diminished T lymphocyte proliferative response to polyclonal mitogens in acute brucellosis patients. Infection (1996) 24:115–119
43. Rodríguez Zapata M, Salmerón I, Manzano L, Salmerón OJ, Prieto A, Alvarez Mon M: Defective interferon gamma production by T lymphocytes from acute brucellosis patients. European Journal of Clinical Investigation (1996) 26:136–140
44. Salmerón I, Rodríguez Zapata M, Salmerón O, Manzano L, Vaquer S, Alvarez Mon M: Impaired activity of natural killer cells in patients with acute brucellosis. Clinical Infectious Diseases (1992) 15:764–770