# Human Brucellosis: Do We Need to Revise Our Therapeutic Policy?

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***ABSTRACT***. ***Objective***. To identify risk factors of relapse among patients with osteoarticular brucellosis.

***Methods***. In a prospective cohort study, we investigated 90 patients with diagnosis of brucellosis, as established by clinical picture and at least 4-fold rise in antibody titer. Osteoarticular involvement was defined by inflammatory signs and radiographic changes. Thirty-five patients received combination therapy of 2 drugs (rifampicin + cotrimoxazole or doxycycline), while 55 patients received a combination of 3 drugs (streptomycin + rifampicin + doxycycline). Monthly followup comprised clinical and laboratory examinations (seroagglutination, IgG, IgM antibody titers). Recovery of patients was based on clinical improvement and seroagglutination antibody titer ≤ 1:80, as well as negative results for IgG and IgM antibody titers. Incidence of relapse was recorded during the 2 year period of followup after finishing the course of treatment.

***Results.*** All patients continued treatment beyond the usual 6 week period previously recommended. Relapse occurred in 59.3% in patients who received treatment for 5 months or less, while relapse occurred in 7.9% among those who received treatment for more than 5 months ($p < 0.001$). Sixty percent of patients who received combination therapy of 2 drugs had relapse, while there was no relapse in patients who received 3 drugs in combination ($p < 0.001$). Logistic regression analysis identified duration of treatment < 5 months and IgG level (above 50 U/ml) as independent predictors for relapse; the predictivity of the model was 85.6%.

***Conclusion***. Extending treatment for longer than previously recommended (6 weeks) resulted in an incidence of relapse significantly lower than for shorter courses of treatment. IgG antibody in addition to seroagglutinating antibody titers are useful for serological followup of patients with brucellosis. (J Rheumatol 2003;30:2666–72)

*Key Indexing Terms:*
BRUCELLOSIS TREATMENT ARTHRITIS

Brucellosis has been an emerging disease since the discovery of *Brucella melitensis* by Bruce in 1887[1]. The disease is distributed worldwide and remains a serious cause of human illness and economic loss, especially in the Mediterranean countries, the Middle East, and Latin America[2]. The natural history of human brucellosis is characterized by the development of relapses after a variable period of clinical latency[3]. *Brucella* is a facultative intracellular pathogen, which seems to account for the high incidence of relapses. The primary goals of therapy for brucellosis are to improve symptoms, reduce complications, and prevent relapse. Despite treatment with several antibiotic regimens, relapse is relatively frequent, and it is estimated that 5–40% of patients with acute brucellosis had relapses at some time during the following year, depending on the antibiotics used, duration of treatment, and combinations of drugs[4,5]. The special characteristics of human brucellosis, which produce relapses and chronic forms of the disease, have important consequences for caring for patients, particularly in the months after therapy[6].

The ability to prevent and/or predict relapse in patients with acute brucellosis has important management and prognostic implications[7]. In most cases, persistence of infection cannot be confirmed by blood cultures or clinical findings only, and serological tests play an important role[8]. However, prospective and longterm followup serological studies in human brucellosis have been scant. Thus some aspects of the serological evolution of brucellosis have not been fully established, especially regarding relapse and/or persistence of infection[9]. We investigated risk factors of relapse in a prospective cohort study of patients with acute brucellosis.

## MATERIALS AND METHODS

*Patients*. We studied 139 patients with diagnosis of brucellosis based on: (1) clinical findings characteristic of the disease[10] and (2) either positive blood cultures for *Brucella* or a tube agglutination titer of > 1:160. Patients were recruited from the rheumatology and rehabilitation outpatient clinics in Insurance Hospital (Riyadh, Saudi Arabia) and Saudi German Hospital (Jeddah, Saudi Arabia). Patients underwent thorough clinical examination:

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osteoarticular complications were considered to be those showing obvious inflammatory signs (hotness, redness, swelling, pain, or limitation of movement) in any peripheral joint, or unrelieved pain at rest in any deep joint with radiographic or gammagraphic evidence, or both. Diagnosis of focal disease, such as epididymo-orchitis, bursitis, or tendinitis, was made on the basis of clinical evidence, e.g., local inflammatory signs at a particular site. No pregnant women or children were included in this study.

*Radiological studies.* A radiographic study of the chest, dorsolumbar spine, and both sacroiliac joints, as well as any other clinically suspected/affected site was conducted in every patient. A radionuclide bone scan with $^{99m}$technetium methylene diphosphonate was performed in cases of inflammatory osteoarticular pain with no radiographically apparent lesion.

*Laboratory studies. Baseline blood tests.* All patients underwent full blood count, erythrocyte sedimentation rate (Westergren method), blood urea nitrogen, serum glucose, creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, protein electrophoresis, and C-reactive protein (nephelometry), in addition to routine urinalysis. These tests were done before starting drug therapy and whenever there was no contraindication, patients started their drug therapy. Patients' blood was checked monthly while they were taking their drug therapy for the same investigation to verify that there were no drug side effects.

*Microbiological studies.* Standard tube agglutination and Coombs' antihuman globulin test were performed using commercial reagents (Wellcome, Dartford, England) according to standard methods[8]. Blood cultures were performed as reported[11] and incubated for 4 weeks using BACTEC 9240 (Becton Dickinson, Mountain View, CA, USA). All isolates were identified as recommended by Shapiro and Wong[12]. Anti-*Brucella* IgG and IgM antibody titers were also assessed in every patient using ELISA (Invitro Diagnostika GmbH, Hamburg, Germany). Blood check for seroagglutination, Coombs' tests, and ELISA for IgG and IgM antibody titer were performed in every patient before starting drug therapy, monthly thereafter until completion of the drug course, and every 2 months thereafter for 24 months.

*Hearing evaluation.* All patients set to receive streptomycin as one of their drugs had a full otological examination, including hearing acuity measurement, prior to commencing and during their drug therapy. Streptomycin therapy was not given if there was a contraindication.

*Type of study.* This was a prospective followup study of patients with a diagnosis of positive brucellosis infection, to determine the relapse rate and factors contributing to its occurrence. To date no intervention has been carried out regarding drug therapy in this condition. Regimens and medications prescribed were tailored to each patient according to his/her condition.

*Therapeutic regimen/management.* All patients were offered treatment with a combination of antibiotics (rifampicin, doxycycline, and streptomycin injections). However, some patients refused streptomycin injection, either because they did not feel able to comply with the frequency of injections or they did not like injection as a treatment option. Thus, the patients were divided at random into 2 groups: (1) 35 patients (Group 1) received 2-drug combination therapy, 17 patients (17/35) received rifampicin, 900 mg/day in a single dose (15 mg/kg per day if body weight was ≤ 50 kg) plus doxycycline, 100 mg twice a day (5 mg/kg per day if body weight was ≤ 40 kg); since 18 women with the disease were of child bearing age and were not taking any contraceptive measures, they were offered drug therapy in the form of rifampicin [900 mg/day in a single dose (15 mg/kg per day if body weight was ≤ 50 kg) plus cotrimoxazole, 960 mg twice daily]. Consultation with a birth control advisor had been arranged for these women. (2) Fifty-five patients (Group 2) received 3-drug combination therapy [streptomycin, 1 g/day intramuscularly for 14 days (15 mg/kg per day if body weight was ≤ 50 kg) plus rifampicin, 900 mg/day in a single dose plus doxycycline 100 mg twice a day]. Drug therapy was continued until seroagglutinating antibody titer reached a level ≤ 1:80, and IgG as well as IgM antibody titers reached levels < 50 U/ml (levels of IgG and IgM antibody titer between 50 and 60 U/ml were considered equivocal, while > 60 U/ml was considered positive). At that stage the treatment course was stopped; patients were then followed up for a period of 24 months.

*Followup.* The patients were assessed initially, on Day 7, and thereafter every month. All patients were informed about the importance of taking the medications regularly as prescribed and of avoiding exposure to possible sources of infection. At each followup visit patients were asked about clinical manifestations of the disease, medication intake, and whether there was any exposure to sources of infection. No patient who continued the followup study reported missed doses or direct exposure to possible sources of infection. Their blood was checked for the routine laboratory studies mentioned above and *Brucella* seroagglutinating antibody titer, as well as IgG and IgM antibody titer. Relapse was defined as recurrence of clinical signs (clinical relapse), in addition to either new positive blood culture (bacterial relapse) and/or a 4-fold increase in serological titer after completion of therapy. At the end of therapy, all patients were followed up every 2 months for 24 months as outpatients, and whenever clinical symptoms reappeared. In addition to clinical examination, patients' blood was checked for *Brucella* seroagglutinating antibody titer as well as IgG and IgM antibody titers. Only 90 patients continued the whole duration of followup (2 yrs). Those who discontinued followup were residing in the countryside, whereas those who completed followup were town residents who were younger than the dropout group and exhibited a change of lifestyle following a change in their main jobs (i.e., they reduced their exposure to animals and other sources of infection).

All patients in this study were informed about the nature of the study and gave consent to participate at the beginning of the study.

*Statistical analysis.* Logarithmic transformation of seroagglutination antigens A and M and IgG and IgM antibody titer was performed to allow better manipulation of data. Student t test was used to compare means between 2 groups. Chi-squared and Fisher-exact tests were used to test association between 2 variables. Mantel-Haenszel test was performed to test linear correlations. Logistic regression analysis was carried out to identify independent risk factors of relapse. All variables that were found to be significantly associated with relapse were reexamined. Highly correlated variables were excluded, i.e., treatment and duration of treatment, clinical and radiological evidence of arthritis. Thus, type of treatment and clinical evidence of arthritis were excluded from the model at beginning of regression. In all tests, type I error (alpha) value was always set at 0.05. All tests were done using the SPSS, Version 6.

## RESULTS

*Study population.* All 139 patients continued their treatment course until their agglutination antibody titer became < 1:80; however, only 90 patients continued for the 2-year followup period. The age of patients ranged between 21 and 57 years. Thirty-eight percent of patients were above 50

*Table 1.* Age and sex distribution of patients with osteoarticular brucellosis.

| | N (%) |
|---|---|
| Age groups | |
| < 30 yrs | 15 (16.7) |
| 30–39 | 30 (33.3) |
| 40–49 | 10 (11.1) |
| 50+ | 35 (38.9) |
| Mean ± SD (range) | 41.6 ± 11.6 (12–57) |
| Sex | |
| Male | 44 (48.9) |
| Female | 46 (51.1) |

years of age and 33.3% were between 30 and 40 years of age. Men were represented almost equally to women, with a sex ratio of 0.95 (Table 1).

On clinical examination, 78/90 (86.7%) and 69/90 (76.7%) of patients had clinical evidence of sacroiliitis and spondylitis, respectively. Twenty patients (27.1%) had other inflammatory articular signs. Multiple joint involvement was frequent. Inflammatory radiological findings were evident in 72.2% of patients. Blood cultures were positive in 70% of the patients. 92.1% of isolated *Brucella* strains were identified as *Brucella melitensis* and 7.9% were *Brucella abortus*.

Thirty-five patients (38.9%) received 2-drug combination therapy, while 55 patients (61.1%) received 3-drug therapy. The duration of treatment ranged between 3 and 8 months (Table 2). Treatment was discontinued based on clinical and laboratory evaluation (see above).

*Treatment, followup, and relapse*. Compliance of patients was relatively good. As about 75% of the subjects included in this study were insured patients, they had to come to the hospital regularly for checkup and to get their medications. Forty-nine of 139 patients (29 from Group 1 and 20 from Group 2) continued their therapeutic course; however, they did not complete the followup period. This was due either to work transfer to outside the city, or because the patients got well and considered followup visits unnecessary. The study was therefore confined to the 90 patients who completed the followup period. Twenty-two out of 90 (22/90) patients preferred to stop treatment when their agglutination antibody titer fell below 1:80, while their IgG and/or IgM antibody titer was equivocal (ranging between 50 and 60 U/ml).

Incidence of relapse among the investigated osteoarticular brucellosis patients was 23.3% over the 2-year followup period. Relapse was 60.0% among patients receiving 2-drug combination therapy, while no case relapsed among those who followed a 3-drug therapeutic regimen (Table 3). There was no significant difference in the incidence of relapse among patients who received rifampicin + doxycycline compared to rifampicin + cotrimoxazole drug therapy (Table 4). Investigating the duration of treatment (Table 3), we noted a significant shift in the incidence of relapse from 66.7% among patients who received treatment for 5 months to 12.5% among those who received the treatment for 6 months. These findings generated the hypothesis of "5 months" as a safe point after which incidence of relapse is very low, compared to its incidence prior to this point.

On studying whether seroagglutinating antibodies could be considered as predictors of relapse, our study revealed a significant difference in the logarithmic levels of these antibodies after 5 months' duration of treatment, while at 3 months from the beginning of therapy there was no significant difference (Table 5).

On comparing the logarithmic levels of seroagglutinating antibodies as well as IgG and IgM antibody titers at the end of therapy, there were significant differences with respect to the type of treatment (i.e., 2-drug vs 3-drug combination — triple drug therapy was significantly lower), duration of treatment (i.e., more vs less than 5 months' duration — duration > 5 months was significantly lower), and relapse (Table 6).

*Table 2*. Joints affected, evident radiological findings, treatment regimen, and incidence of relapse among patients with osteoarticular brucellosis.

| | N (%) |
|---|---|
| Joints affected | |
| Sacroiliitis | 69 (76.7) |
| Spondylitis | 78 (86.7) |
| Other arthritis | 20 (22.2) |
| Positive radiological findings | 65 (72.2) |
| Treatment regimen | |
| Medications | |
| Rif + Cotrim or Doxy | 35 (38.9) |
| Rif + Strept + Doxy | 55 (61.1) |
| Duration of treatment, mo | |
| 3 | 7 (7.8) |
| 4 | 11 (12.2) |
| 5 | 9 (10.0) |
| 6 | 40 (44.4) |
| 7 | 15 (16.7) |
| 8 | 8 (8.9) |
| Relapse | 21 (23.3) |

For definitions see Table 3.

*Table 3*. Incidence of relapse in relation to type and duration of treatment regimen.

| | Relapse | | |
|---|---|---|---|
| | Yes (%) | No (%) | p |
| Type of treatment | | | |
| Rif + Cotrim or Doxy | 21 (60.0) | 14 (40.0) | |
| Rif + Strept + Doxy | 0 (0.0) | 55 (100.0) | < 0.001* |
| Duration of treatment, mo | | | |
| 3 | 4 (57.1) | 3 (42.9) | |
| 4 | 6 (54.5) | 5 (45.5) | |
| 5 | 6 (66.7) | 3 (33.3) | |
| 6 | 5 (12.5)† | 35 (87.5) | |
| 7 | 0 (0.0) | 15 (100.0) | |
| 8 | 0 (0.0) | 8 (100.0) | < 0.001* |

† Significant reversed incidence of relapse at 6 mo duration of treatment. * Highly significant. Values in parentheses are percentages from rows. Rif: rifampicin, Cotrim: cotrimoxazole, Doxy: doxycycline, Strept: streptomycin.

*Table 4*. Incidence of relapse among patients who received rifampicin + doxycycline compared to those who received rifampicin + cotrimoxazole.

| Variable | RIF + Doxy Group, No. of Patients (%) | Rif + Cotrim Group, No. of Patients (%) | p |
|---|---|---|---|
| No relapse | 7/17 (41.2) | 7/18 (38.9) | 0.89 |
| Relapse | 10/17 (58.8) | 11/18 (61.1) | 0.87 |

*Table 5.* Different logarithmic levels of seroagglutinating antibody titers at 3 and 5 months Followup in relation to incidence of relapse.

| | Relapse | | | | |
|---|---|---|---|---|---|
| | N | Yes (mean ± SD) | N | No (mean ± SD) | p |
| 3 months | 21 | 5.04 ± 0.6 | 65 | 5.32 ± 0.7 | 0.07† |
| 5 months | 10 | 4.24 ± 0.3 | 59 | 4.66 ± 0.7 | 0.003* |

SD: standard deviation. * significant; † not significant.

Patients who presented with sacroiliitis reported a higher incidence of relapse (29.0%) than those with no sacroiliitis (4.8%). The same findings were evident with spondylitis, where 26.9% of patients with spondylitis relapsed versus no patient without spondylitis. Positive radiological findings were associated with relapse in 32.3% of patients versus no patient without radiological findings (Table 7).

Women reported a higher incidence of relapse (34.8%) than men (11.4%). Regarding age, the age group 30–40 years reported the highest incidence of relapse (36.7%) followed by the age group 50+. The age group "below 30 years" (n = 15) reported no relapses over the 2-year followup period (Table 7).

Twenty-two patients reported an IgG level below 60 U/ml but above 50 (equivocal); 68.2% of them relapsed compared to 8.8% among those who reported an IgG level below 50 (negative). The same finding was evident with IgM: 72.7% of patients with equivocal IgM antibody titer relapsed compared to 16.5% among patients with frank negative (below 50) IgM antibody levels (Table 8).

Based on logistic regression analysis, the independent risk factors for relapse in patients with osteoarticular brucellosis who were investigated were: duration of treatment (3-drug combination therapy) and IgG level at the end of therapy (frank negative), with a predictivity of 85.6% (Table 9).

*Table 7.* Association of relapse with age groups, sex, joint involvement, and radiological evidence.

| | Relapse* | | |
|---|---|---|---|
| | Yes, (%)† | No (%)† | p |
| Age groups | | | |
| < 30 yrs | 0 (0.0) | 15 (100.0) | |
| 30–39 | 11 (36.7) | 19 (63.3) | |
| 40–49 | 1 (10.0) | 9 (90.0) | |
| 50+ | 9 (25.7) | 26 (74.3) | 0.034**† |
| Sex | | | |
| Male | 5 (11.4) | 39 (88.6) | |
| Female | 16 (34.8) | 30 (65.2) | 0.017** |
| Joint involvement | | | |
| Sacroiliitis | | | |
| Present | 20 (29.0) | 49 (71.0) | |
| Absent | 1 (4.8) | 20 (95.2) | 0.02** |
| Spondylitis | | | |
| Present | 21 (26.9) | 57 (73.1) | |
| Absent | 0 (0.0) | 12 (100.0) | 0.06*** |
| Radiological findings | | | |
| Negative | 0 (0.0) | 25 (100.0) | |
| Positive | 21 (32.3) | 44 (67.7) | 0.003** |

* Percentages are from rows. ** Significant; *** Not significant. † Pearson chi-squared test was statistically significant, but Mantel-Haenszel for linear association was not.

## DISCUSSION

Despite extensive studies over the past 15 years, the optimum antibiotic therapy for brucellosis is still disputed. The treatment recommended by the World Health Organization (WHO) for acute brucellosis in adults is rifampicin (600–900 mg) and doxycycline (200 mg daily) for a minimum of 6 weeks[2]. However, other studies reported that the long established combination of intramuscular streptomycin with an oral tetracycline and continuation of doxycycline for up to 2 months in cases of osteoarticular and visceral complications gives better results and fewer relapses[13-16].

Previous pathological data showed that *Brucella* is localized intracellulary and is therefore relatively inaccessible to antimicrobials[17,18]. In addition, the results of animal studies revealed that, when animals were infected with the *Brucella* microorganism and immediately treated with antibiotics, although the infections were suppressed, the microorganisms were not eradicated completely from tissues[6]. Moreover, previous studies indicate that prolonged course of antibiotic therapy is recommended to eradicate *Brucella* from the tissues[19-21]. These data suggested that to eradicate

*Table 6.* Different logarithmic levels of seroagglutinating, IgG, and IgM antibody titer at the end of treatment in relation to type, duration of treatment, and relapse. Values are mean ± SD.

| | Type of Treatment | | Duration of Treatment | | Relapse | |
|---|---|---|---|---|---|---|
| | Double† | Triple‡ | Less than 5 mo | More than 5 mo | Yes | No |
| Antibodies | | | | | | |
| Seroagglutinating | 4.28 ± 0.3** | 3.99 ± 0.4 | 4.25 ± 0.4* | 4.04 ± 0.3 | 4.35 ± 0.3** | 4.03 ± 0.4 |
| IgG | 3.87 ± 0.1** | 3.82 ± 0.0 | 3.88 ± 0.1** | 3.83 ± 0.1 | 3.89 ± 0.1** | 3.83 ± 0.1 |
| IgM | 3.85 ± 0.1** | 3.77 ± 0.1 | 3.85 ± 0.1* | 3.78 ± 0.1 | 3.88 ± 0.1** | 3.78 ± 0.1 |

* Statistically significant difference, $p < 0.05$. ** Statistically significant difference, $p < 0.001$. † Combination of rifampicin and cotrimoxazole or doxycycline. ‡ Combination of rifampicin, doxycycline, and streptomycin.

*Table 8.* Negative versus equivocal IgG and IgM antibody levels at the end of treatment in relation to incidence of relapse.

| | Relapse | | |
|---|---|---|---|
| | Yes, (%)* | No, (%)* | p |
| IgG | | | |
| Negative | 6 (8.8) | 62 (91.2) | |
| Equivocal | 15 (68.2) | 7 (31.8) | < 0.001† |
| IgM | | | |
| Negative | 13 (16.5) | 66 (83.5) | |
| Equivocal | 8 (72.7) | 3 (27.3) | < 0.001† |

* Percentages are from rows. † Highly significant.

*Brucella* infection and prevent its relapse or treatment failure, brucellosis infection should be treated by combination drug therapy and for long duration.

Our study shows that longer treatment course is associated with lower incidence of relapse. A 3-drug combination also gave lower risk of relapse than the 2-drug combination. The combination therapy that was used for treatment of *Brucella* in our patients was the most accepted one internationally. The treatment recommended by the WHO for acute brucellosis in adults is a combination of rifampicin and doxycycline daily for a minimum of 6 weeks[22]. However, it has been reported that a combination of tetracycline and an aminoglycoside remains the most effective regimen because of its synergistic effect. Oral doxycycline is preferred to other tetracyclines because of its rapid and complete absorption from the duodenum, longer half-life (18–22 h), and more efficient tissue penetration as it is more lipid soluble[23,24]. Earlier studies showed that the combination regimen of doxycycline and an aminoglycoside for 1 month, followed by doxycycline and rifampicin or doxycycline and cotrimoxazole for a further 1 to 2 months, resulted in a relapse rate of 7%[25]. As fluoroquinolones and third-generation cephalosporins (e.g., ceftriaxone) are still controversial for use in brucellosis[22,26-28], we were reluctant to treat our patients with new combinations, preferring drug combinations that are considered to be the most accepted regimens internationally.

On admission, all our patients had elevated antibody titers detectable by the agglutination test, Coombs' test, and IgG and IgM ELISA tests. This finding agrees with the results reported by Ariza, *et al* and Araj, *et al*[9,29], who found that the IgG, IgM, and IgA levels as measured by ELISA showed a high degree of correlation and strong, statistically significant independent relations to titers measured by tube agglutination tests. However, in studies by Reddin, *et al*[30] and by Buchanan and Faber[31], they found slower development of IgG *Brucella* antibody titer in their group of patients. In fact, the early production of IgG antibody to *Brucella* in humans is in accordance with the pattern of IgG production in experimental brucellosis in mice[32] and with the results of earlier studies[9,29].

In our patients who did not experience a relapse of brucellosis, serum antibody titers in the various tests decreased significantly during the first months of illness. ELISA IgM titers then decreased further, followed by ELISA IgG titers. These data agree with the most recent reports on the determination of specific immunoglobulins[29,33-38], but contrast with the experience of other investigators, who reported a more prolonged persistence of non-IgG agglutinating antibodies[30]. However, our observation was confirmed by the finding that, in the patient group who experienced relapse, the antibody titer decreased in the same pattern when they received the new course of antibiotic therapy.

The evaluation of longterm persistence of high titers of a serum antibody is still a matter of debate. The significance of this finding is difficult to establish because the time of total intracellular eradication of *Brucella* in a particular case cannot be known with certainty, and no accurate criteria for complete cure exist. We believe that persistent elevation of antibody titers for a prolonged time after stopping treatment, despite the absence of systemic manifestations, is an indicator of persistent infection, and the possibility of relapse in such a group of patients is very high. Further, results of this study showed that even equivocal IgG and IgM levels at the end of therapy were significantly associated with a higher incidence of relapse than those who reported negative levels of these antibodies at the end of treatment.

The results of our study show that in the majority of relapsed patients a significant increase of serological variations could be detected. Although the time at which the

*Table 9.* Results of logistic regression analysis for prediction of risk factors of relapse among patients with osteoarticular brucellosis.

| | Regression Coefficient | Wald Test | SE | Significance | OR |
|---|---|---|---|---|---|
| Variables in the equation | | | | | |
| IgG (equivocal vs negative)† | 2.34 | 11.46 | 0.69 | < 0.001 | 10.3 |
| Duration of treatment, < 5 vs > 5 mo | 2.01 | 8.58 | 0.69 | < 0.001 | 7.5 |
| Constant | | | –2.24 | | |
| Predictivity of the model, % | | | 85.6 | | |

† IgG and IgM antibody titer is considered negative if < 50 U/ml, equivocal if between 50 and 60 U/ml, and positive if > 60. SE: standard error; OR: odds ratio.

serology varied differed from one patient to another, in all patients this variation was the consequence of a second peak in the level of IgG antibody and, to a lesser extent, increased IgM. The rise of agglutinating antibody titer was most marked during the 3 months after relapse. Our results are in agreement with the most widespread opinion concerning the relevance of IgG antibodies as indicative of active infection[30,31,39-41]. However, some authors suggest that a relapse of the disease is associated with elevation of titers of both IgM and IgG to *Brucella*[42,43].

The rationale of continuous antibiotic therapeutic course is that, based on the literature, it is always advisable to treat an infection completely rather than wait for relapse, which will be treated thereafter. Moreover, the possibility of chronic infection, especially if the compliance of the patient is poor, should be considered carefully. Hence, it is recommended to deal with the cases more aggressively from the therapeutic point of view in a trial in order to achieve absolute eradication of the infection. Mousa, *et al*[44] suggested interrupted antibiotic courses for treatment of osteoarticular brucellosis. Considering that relapses in brucellosis rarely occur less than 4 weeks after completion of antibiotic course, patients with spondylitis, arthritis, osteomyelitis, or meningitis in their study received 4 courses of antibiotic therapy, with a 4-week rest period between each course. However, interestingly, good results were obtained in 7 cases of osteomyelitis receiving continuous antibiotic therapy for > 12 weeks. Further studies are needed to confirm the efficacy of different regimens and to determine which of them would best reduce relapse for more prolonged periods.

In conclusion, 3-drug combination therapy and treatment for longer duration than previously recommended (6 weeks) resulted in significantly lower incidence of relapse than 2-drug combination therapy or short courses of treatment. IgG antibody and seroagglutinating antibody titers are useful for the serological followup of patients with brucellosis. IgG antibody is the best predictor of relapse.

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