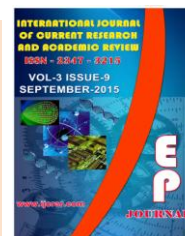




International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 3 Number 9 (September-2015) pp. 259-265

www.ijcrar.com



Evaluation relapse rate of brucellosis and efficacy of therapeutic regimens

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KEYWORDS

Brucellosis,
Relapse Rate,
Therapeutic
Regimens,
Efficacy

A B S T R A C T

Brucellosis is a disease that is between human and the sheep's and you can find it all over the world. The etiologic agent of disease is an intracellular organism that attacks different organs in the body and can show wide clinical pictures. The treatment of the brucellosis has to control the disease and avoids the future problems and the relapse of the disease. Because this organism is intracellular, sometimes hides from the affect of the drugs and it may relapse after the specific clinical treatment: because this disease is common in our country we make this study to know demographic pictures, the way of the transport of the disease, the most common complications when the patients come, the laboratory abnormalities, the most effective treatment diet that can control the disease and avoids the disease to relapse, specially. The aim of this study is comparison between classic therapeutic regimens of brucellosis for relapsing rate after treatment. In this clinical-trial and prospective study that longed for one year, all the patients that diagnosed as brucellosis and admitted in the Bu-Ali Sina teaching hospital in Qazvin and that patients with brucellosis refer to the outpatients clinic of Bu-Ali Sina teaching hospital gone under study. 214 patients were collected and according to their conditions, divided to 3 therapeutic groups: Group A (Streptomycin or Gentamicin plus Doxycycline), Group B (Co-trimoxazole plus Rifampin), Group C (Doxycycline + Rifampin). After complete treatment, the patients follow up for relapsing for 3 months and because of special goals, our information's collected and the results become. The males are the most common in this disease and the most age period is between 13-30 years old. Most of the patients are from the village and the common way of transportation of this disease is dairy products and after that closing to the animals. The most symptoms are fever and chill, sweating, arthralgia, low back pain, joint pain. The most signs are bone and joint problems like sacroiliitis and peripheral joint arthritis. From the 214 patients under treatment, the relapse rate after regimen A was 7.6%, after regimen B was 6%, and after regimen C was 10.5%. The most rate of relapse was in females and in ages 61y. The most rate of relapse opposite to our expectation was in citizen and in high educated level patients. Base on our statically results, the choice therapeutic diet according to relapse rate, treatment duration and cost is Doxycycline plus streptomycin or Gentamicin and the alternative treatment is co-trimoxazole plus Rifampin (in selected cases such as children under eight years and pregnant women specially), also the third regimen (Rifampin plus Doxycycline) according to higher relapse rate and complications is not recommended.

Introduction

Brucellosis is the most important common infectious disease between humans and livestock (1) which is currently regarded as a global problem (2). It can be found in all countries in the Eastern Mediterranean Region as well as the Middle East with the exception of Cyprus. In Iran, *Brucella Abortus* and *Melitensis* infections are common (1).

Before 1989, the annual incidence of human brucellosis in Iran experienced an uptrend, while it saw a downtrend from 1989-2000. Unfortunately, the number of human cases with brucellosis has been rising again in recent years.

Due to the flourishing of livestock breeding in the spring the incidence of this disease is higher in this season. This can be reduced by livestock vaccination, leading to an eventual decrease in the incidence of human transmission. The transmission of this disease to humans occurs as a result of the consumption of infected animal products such as milk, cheese, and yogurt, or by direct contact with infected animals which could bring about non-specific symptoms. According to Simpson: "No disease, not excepting syphilis and tuberculosis is more protean in its manifestations" (3-4). Humans have a marginal role in maintaining this disease in nature (5).

The aim of this study was to determine the relapse rate of brucellosis and the efficacy of various therapeutic regimens in outpatients and inpatients admitted to Qazvin Bu-Ali hospital.

Methods and Materials

In a clinical trial conducted on patients with brucellosis in Qazvin, Iran, the relapse rate

of this disease and the efficacy of various therapeutic regimens in outpatients and inpatients admitted to Qazvin Bu-Ali Sina teaching hospital were investigated.

Relapse was determined based on the recurrence of brucellosis symptoms as well as a positive 2-mercaptoethanol (2 ME) titer. A positive 2 ME titer without the recurrence of brucellosis symptoms was not regarded as a case of relapse (6).

In view of the general and specific objectives of the study, a questionnaire was prepared. All patients admitted to the infectious diseases clinic as well as those hospitalized in the Infectious Diseases ward for brucellosis (based on clinical and laboratory findings), filled the questionnaire after the definite diagnosis by an Infectious Disease (ID) specialist. Such information as demographic information, disease transmission ways, the symptoms based on their medical history as well as the examined complications upon their admission, the type of therapeutic treatment administered to them, laboratory information, and so on were recorded.

Specific tests carried out on patients suspected with brucellosis included Wright and Coombs-Wright tests. Active cases of brucellosis were diagnosed in terms of contact history, clinical and physical symptoms, and increased levels of *Brucella* agglutination. It should be noted that, Wright agglutination titers of $\geq 1/80$ were considered as positive tests of *Brucella* (4). However, Coombs-Wright tests were also carried out on patients whose Wright titers were lower than 1/80 and whose clinical symptoms corresponded to those of brucellosis. They, then, received treatment in cases where high amounts of titer were reported.

In any case, patients were treated with one of the following three therapeutic regimens: regimen A (streptomycin or Gentamicin for 3 or 2 weeks, respectively + Doxycycline for 6 weeks), regimen B (Co-trimoxazole for 3 weeks + Rifampin for 6 weeks), and regimen C (Doxycycline + Rifampin for 6 weeks). Patients who had not developed any complications and those with onsets of less than a month underwent treatment for 6 weeks, and those with disease courses of more than one month received treatment for about 8-12 weeks.

It is worth mentioning that the recommended regimen to the patients in this study was regimen A, as it is the preferred regimen of treating brucellosis in the majority of studies and specialized medical textbooks (6). However, since regimen A involved injections to be administered for 2-3 weeks, some patients opted for regimen C, which was oral. Given the side effects of Doxycycline, streptomycin and Gentamicin, regimen B was recommended to pregnant women and children under 8 years of age. Therefore, with the exception of regimen B, the treatment of patients was completely non-compulsory. Accordingly, the patients were divided into 3 groups. The patients were tracked during and after the course of treatment. In the event that evidence pointed to relapse, 2 ME tests were requested for patients. If the results were positive ($\geq 1/40$) the condition was regarded as a case of brucellosis relapse and the patients were treated again for another course.

Problems and Limitations

1) Lack of easy access to patients in order to continue clinical observations as a result of not having access to telephones, living in rural areas, etc., with some patients excluded from the study because of this.

- 2) Rapid recovery of patients after receiving treatment and not referring back to the hospital in order for their possible relapses to be examined, with some patients excluded from the study as a result of this.
- 3) Since a great number of patients were among those who lived in rural areas with lower-income backgrounds, some limitations were experienced in utilizing diagnostic facilities such as specialized tests, medical ultrasound, hospitalization, etc.
- 4) Illiteracy or low education levels on the part of the majority of patients that inhibited persuading them to cooperate.
- 5) Low socio-cultural levels on the part of some patients in presenting their full medical history, and the related problems to tracking patients.

Statistical Analysis

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean \pm SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤ 0.05 was considered statistically significant.

Results and Discussion

In this study, the total number of examined cases was 214 individuals, i.e. 128 (59.8%) were male and the rest were female. 105 (49.5%) of patients had professions that were related to brucellosis, such as farming, animal husbandry, shepherding, and rural housekeeping. 135 (63.1%) of patients lived in rural areas and the rest in cities. In addition, 70 (32.7%) of patients were uneducated, 104 (48.6%) had lower-than-

diploma education, and 40 (18.7%) had high school diplomas or above-than-diploma education.

In terms of medical history, the most common ways of disease transmission were the consumption of raw dairy products such as local cheese and cream seen in 188 (89.7%), and direct contact with animals in 129 (60.3%) of patients. Other least common ways of transmission included history of skin pricks in 10 (4.7%) and the consumption of raw meat in 11 (5.1%) of patients.

The most common clinical symptoms were arthralgia in 158 (73.8%), back and joint pain in 151 (70.6%), perspiration in 150 (70.1%) and chills in 143 (66.8%) of patients, respectively.

The most common complication upon admission was joint and bone troubles, in particular, sacroiliitis and osteoarthritis of the peripheral joint in 26.2% (56) of patients. Other complications included genitourinary complications (epididymo-orchitis) in 8.4% (18), Splenomegaly in 8% (17), hepatic complications in 1.9% (4), neurological complications (meningitis) in 0.9% (2) and endocarditis in 0.5% (1) of the patients.

In terms of the therapeutic regimen types and responses to them, of the 214 examined patients, 106, 52, and 58 patients underwent regimen A, B, and C, respectively. The relapse rates for regimens A, B, and C were 7.6%, 6% and 10.5%, respectively ($P = 0.675$).

The highest relapse rate in terms of sex belonged to females with 7 (8.1%) cases ($P = 0.975$) and to higher than 61 years in terms of age with 5 (11.6%) cases ($P = 0.818$).

From the occupational perspective, the relapse rate was 6 (5.7%) cases in the population of farmers, livestock breeders, and shepherders, and 11 (10.2%) cases in other occupational populations ($P = 0.211$).

In terms of place of residence, 9 (11.5%) and 8 (6%) cases of relapse were reported in urban and rural populations, respectively ($P = 0.15$).

In terms of education level, the relapse rate among uneducated individuals was reported to be 4 (5.8%) cases, 5 (4.9%) cases among lower-than-diploma levels, and 8 (20%) among diploma or above levels ($P = 0.008$).

In terms of laboratory findings, anemia and leukopenia were observed in 28 (23.3%) and 4 (3.33%) of patients, respectively. High Erythrocyte Sedimentation Rate (ESR) and positive C - reactive protein (CRP) results were also seen in 43 (35.8%) and 26 (21.6%) of the patients, respectively. Wright-test was negative in 30 (14%) of patients and Coombs-Wright test was positive in all patients.

In this study, the total number of examined patients within the specified period was 214, with the highest incidence of disease belonging to males (59.8%) and the 13-30 age group (38.7%). 49.5% of patients had direct contact with livestock in one way or another. Furthermore, in terms of education, the highest incidence of brucellosis belonged to uneducated or those with lower levels of education as well as to residents of rural areas.

In a study conducted in Maghdonieh, the highest incidence belonged to the 21-30 age group, females, and residents of rural areas (7).

In another study carried out in Kayseri, Turkey, the highest and lowest incidence in terms of age group belonged to the 11-20

and 31-40 ones, respectively. Males had the highest level of involvement (8).

In yet another research undertaken in Athens, Greece, the highest incidence belonged to uneducated individuals and 56.8% of the diseased were engaged in occupations that were related to livestock (9).

In our study, the most common transmission ways were the consumption of raw unpasteurized dairy products such as local cheese and cream. Following that is direct contact with animals, with the least common way of transmission being having a history of skin pricks and the consumption of raw meat.

In the study conducted in Hamadan, Iran, the most common way of transmission was the consumption of infected raw dairy products. 83.96% of patients had a history of direct contact with livestock or their viscera (10).

In the study of Gerald Emaloney, the most common way of contracting the disease was similarly reported (11). In our research, the most common symptoms were arthralgia, back and joint pain, perspiration and chills, respectively.

In a study conducted in Athens, Greece, the majority of patients with brucellosis experienced musculoskeletal symptoms and fever (9). In another research in Macedonia, the most frequent clinical symptoms were arthralgia, perspiration, and fever, respectively (7).

The most common complications in our study upon admission were joint and bone troubles, in particular, sacroiliitis and osteoarthritis at the peripheral joint with an approximate prevalence rate of 26.2% for each. The incidence of genitourinary

complications (epididymo-orchitis), hepatic complications, neurological complications (meningitis), and endocarditis were 8.4%, 1.9%, 0.9%, and 0.5%, respectively. In addition, the incidence of Splenomegaly in our study was lower than that in the studies cited below (7.9%) which was probably due to not utilizing imaging methods for diagnostic purposes on account of their high economic burden.

Arthralgia, physical skeletal-oriented and environmental findings are found in 40% of cases. Hepatomegaly and Splenomegaly, endocarditis, and epididymo-orchitis are observed in 25%, 1%, and 10% of cases (6), which, with the exception of Splenomegaly correspond to the findings of the present study.

Gastrointestinal, skeletal, Central Nervous System (CNS), endocarditis, orchitis, and Splenomegaly or Hepatomegaly symptoms are found in 70%, 20-60%, less than 5%, 2%, 20% of males, and 20-30% of patients, respectively (12).

In terms of therapeutic regimen types and responses to them, the relapse rates for regimens A, B, and C were 7.6%, 6%, and 10.5%, respectively. Considering the insignificant difference between regimens A and B, treatment costs, and the use of Rifampin in other therapeutic cases such as for treating tuberculosis, and the necessity of adopting resistance preventive measures to it, the best therapeutic regimen is A. In another study conducted at Babol University of Medical Sciences, the relapse rates for regimens A, B, and C were reported to be 34%, 12.7%, and 9.8%, with regimen C selected as the recommended regimen (13).

In the study carried out at Hamedan University of Medical Sciences, the relapse rates for regimens A and B were reported to be 5.7% and 9.3%, respectively, based on which regimen B plus Amikacin was

recommended to reduce the relapse rate (12).

In the study undertaken by Acocella et al., the cure rates for regimens A (Rifampin + Doxycycline), B (Doxycycline + Streptomycin), and C (tetracycline + Streptomycin) were 95%, 96%, and 51%, respectively, suggesting that the first two regimens had similar effects and that the third regimen should not be used as the selected treatment (14).

In the study conducted by Colmenero-Castillo et al., the relapse rate for the therapeutic regimen consisting of Rifampin + Doxycycline and the Doxycycline + streptomycin regimen was reported to be 13.46% and 8.4%, respectively. It was, therefore, concluded that the Rifampin + Doxycycline regimen could be used as an alternative treatment rather than the treatment of choice in treating human brucellosis (15).

In addition, in this study, the relapse rate for patients living in rural areas and with lower levels of education was, unexpectedly, lower than those living in cities and with higher levels of education. This could probably be accounted for by the negligence and lack of sensitivity shown to brucellosis relapse symptoms on the part of rural area residents with lower levels of education. In any event, given the limited number of studies done in this regard, it appears that it is necessary for more researches to be conducted in order to yield more adequate results.

Suggestions

In light of the results of the present study and its comparison with those obtained from other researches, the following suggestions could be put forwards:

- The best therapeutic regimen for treating human brucellosis is the one containing

Streptomycin (for 3 weeks) or Gentamicin (2 weeks) + Doxycycline (6 weeks); and Co-trimoxazole (for 3 weeks) + Rifampin (for 6 weeks) as the alternative regimen.

- Considering that the highest incidence occurs during active vocational and economic years, disease prevention becomes particularly important. Since the majority of patients from rural communities were in direct contact with livestock and unpasteurized dairy animal products, the following strategies are recommended for the primary prevention of brucellosis:
 - The identification of infected animals, using serologic tests, and isolation them from the rest of animals.
 - The vaccination of eligible animals.
 - Offering general education programs about the disease and preventive measures thereof to vulnerable individuals and to the general public in endemic regions.
 - Pasteurization of dairy products.
 - Refraining from consuming raw animal products, touching infected carcasses; using gloves and protective glasses during occupational contacts.
 - Educating clergymen and local teachers and seeking their assistance in raising the awareness of local people about the disease and preventive measures thereof.
 - Insuring livestock, delivering healthy livestock for infected ones, indemnifying farmers and livestock breeders for their loss.
 - The coordination of city disease units with their respective health units; performing inspections of all production and distribution centers of dairy products. The removal of cream separator devices from all yogurt making centers; prevention of yogurt distribution in bulk.
 - The coordination of all city centers with the Veterinary Office to arrange

inspections of different city parts for the timely report of brucellosis outbreaks, and for the inspecting of meat shops, abattoirs, and milk collection and distribution centers.

- Coordinating with urban and rural water and wastewater offices, telecommunications and power departments to include pre-determined slogans for the world-zoonosis-day in the header of bills and official correspondence.

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