

# **Clinical Course and Treatment of Human Brucellosis in a Sample of Hospitalized Cases in Albania**

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## **Abstract**

Brucellosis remains a public health problem in many Mediterranean countries. In this work are presenting data of human brucellosis clinics and treatment in a sample of hospitalized patients. Methods: All patient charts at regional hospital in Gjirokastra, Albania were systematically reviewed, during the period 2016-2021. All hospitalized patients with a laboratory confirmed diagnoses of brucellosis were included in the study. Variables of interest were clinical symptoms, clinical course and treatment provided. Sub-acute brucellosis was defined as clinical persistence of 3-12 months while cases with clinical symptoms persisting for  $\geq 12$  months were defined as chronic brucellosis. Results: 79% of the 86 patients were male and residing in rural areas. Fever, profuse sweating and arthralgia were the most common clinical signs. Around 70% of the brucellosis patients showed all these three symptoms. Despite a systematic tendency for more frequent presence of high fever, increased sweating and arthralgia on younger patients we could not find statistically significant differences among demographic categories. 18.6% of cases presented persistence of clinical signs after at least 3 months from the moment of the diagnoses. Almost 7% of the cases were classified as chronic cases. 75.6% of all patients were treated with a combination of doxycycline and ceftriaxone antibiotic regime. Conclusions: The massive use of a cephalosporin in treatment of brucellosis cannot be justified and may reflect a larger problem related to population awareness and health provider attitudes concerning antibiotic use in Albania. The results of this study may assist future interventions to improve brucellosis case management at hospitals or primary health care level as well as national measures at a larger scale for control of the disease.

**Keywords:** Brucellosis, treatment, antibiotic, Albania

## Introduction

Although brucellosis is eradicated in many high-income countries, it remains a common disease in humans and animals in most countries of Eastern Mediterranean.

Humans are infected by direct contact with animal tissues or indirectly by consumption of infected animal foods such as meat or dairy. The aerosolized particles containing the brucellae bacteria can also be inhaled by people manipulating the contaminated products (1). Most cases are caused by unpasteurized goat or sheep milk or cheese. Person to person transmission, although rare, is also reported. Brucellosis is considered an occupational hazard to people engaged in certain professions such as veterinarians, slaughterhouse workers, and farmers (2).

The disease may take acute, or chronic forms and usually causes weakness, headache, lethargy, weight loss, fever, and sweating. The fever is typically remittent, giving the disease the name, undulant fever (3,4). Fever with unknown origin, which is the main symptom of brucellosis; can be misdiagnosed with similar pathologies including all fevers of unknown origin that may be caused by infectious diseases such as leishmaniasis, tuberculosis, malaria, as well as other diseases such as malignancies, rheumatic fever etc (5).

The incubation period is usually from 2 to 4 weeks, but may be highly variable. The forms of the clinical course of brucellosis in humans are categorized as acute, sub-acute and chronic (6).

The diagnosis of chronic brucellosis is often based on clinical complaints together with the presence of high immunoglobulin G titers (7).

Treatment in human brucellosis is done by use of a combination of antibiotics. Because the bacteria reside within cells, several weeks of treatment are needed. Treating with a single antibiotic is not recommended as there is a high rate of relapse when a combination regimen is not used (8)

The brucellae are gram-negative aerobic coccobacilli with *brucella melitensis* the most prevalent species mostly because of difficulties in immunizing goats and sheep (9).

The common reservoirs for Brucellae bacteria that may infect humans are cattle, dogs, sheep, goats, and pigs. Brucellosis remains an important public health problem and being a zoonotic disease, its control in humans implies preventive measures of a veterinary nature.

Although under control during recent years, the brucellosis is far from being eradicated in Albania, with cases reported from more than half of administrative municipalities. Since 30 years ago, the incidence of brucellosis has appeared to be higher in the Southern and Southeastern parts of the country. The risk of infection in the Vlorë, Gjirokastër, and Korçë counties has been significantly higher compared to other parts of Albania (10).

Although well studied in global level, publications about brucellosis clinical characteristics and treatment in Albania are scarce. We have not found any peer reviewed documents during the last decade to describe brucellosis characteristics and treatment in the South of Albania where the risk remains high. The aim of this work is to present data of human brucellosis clinical course in hospitalized patients as well as patterns of treatment of the disease. We compare the data to international clinical profiles and treatment protocols.

## Methods

For this study we systematically reviewed all patient charts at Regional Hospital in Gjirokastra, Albania during the period 2016-2021. All hospitalized patients who had a laboratory confirmed diagnoses of brucellosis are included in the study. Laboratory test applied for the diagnoses confirmation has been Wright agglutination essay. This test has been validated and used to assist clinical management of cases (11,12) and epidemiological surveillance.

Although microbiological tests such as isolation of *Brucella* spp. and molecular tests are recommended in brucellosis confirmation, these tests were not available in Gjirokastra hospital.

The clinical chart included data about age, sex and residence of the cases, as well as clinical symptoms, clinical course and treatment provided. All these variables were used for the analyses. Chronic brucellosis was defined as clinical symptoms persisting for  $\geq 12$  months (13). A sub-acute category was also added as clinical persistence of 3-12 months (6).

The systematic search was done in statistical unit of the Hospital and an excel matrix was used to retrieve the data from the individual charts

Data were analysed in SPSS software package. When necessary, 95% confidence intervals were applied.

## Results

There were 86 patients identified during the systematic search of the period 2016-2021 in the Gjirokastra Regional Hospital. 67 cases were males and 19 cases females, which represents a more than three times risk difference. Almost the same difference was observed between rural and urban residency of patients; 68 cases were from rural areas, in a region where rural and urban populations are similar (Census 2011). The highest number of reported cases during the period of study belonged to the age category of 40-60 years old (32 cases). 23 cases were young adults of age 18-39 years old and 25 cases were over 60 years old. There were only 6 brucellosis cases reported in children and teenagers. No cases under the age of 10 were identified.

Not all of the cases were presented with fever as a symptom of brucellosis. Still, fever along with profuse sweating and arthralgia were the most common clinical signs of brucellosis in Gjirokastra hospital. Around 70% of the brucellosis patients showed all

these three symptoms. Additionally, other relatively common symptoms which have been seen in about 20% of the cases were weakness, back pain and muscle pain referred in clinical charts as myalgia.

Frequency of brucellosis symptoms among hospitalized patients is presented in the Table 1.

Table 1. Symptoms of Brucellosis cases

Symptoms	Cases	%
Fever	63	73%
Sweating	61	71%
Arthralgia	59	68%
Lumbalgia	17	20%
Weakness	16	18%
Myalgia	16	18%
Frissons	9	10%
Headache	9	10%
Nausea	9	10%
Dyspnea	6	7%
Cough	6	7%
Anorexia	4	5%
Stomach ache	3	4%

Note: More than one symptom could be reported in each of the patients.

Distribution of brucellosis clinical signs according to sex, age-groups and residence are presented in Table 2. In young people, there is a systematic tendency of a relatively more frequent presence of high fever, increased sweating and arthralgia. On the other hand, some clinical signs such as lumbalgia, and to a certain degree myalgia (data not shown), were found systematically more often among older patients compared to younger ones. Arthralgia in females seemed to be more common than fever or sweat, compared to males.

Nevertheless, despite all those observed tendencies, our sample failed to prove that the differences were of statistical significance as shown by broad 95% confidence intervals.

Table 2. Most common symptoms distributed according to sex, age and residency

	Fever		Sweating		Arthralgia		Lumbalgia	
	Cases (%)	95% IC	Cases (%)	95% IC	Cases (%)	95% IC	Cases (%)	95% IC
<b>Sex</b>								
Males	52 (78%)	66%-86%	48 (72%)	59%-81%	44 (66%)	53%-76%	15 (22%)	14%-33%
Females	11 (58%)	36%-76%	13 (68%)	40%-84%	15 (79%)	57%-91%	2 (11%)	2%-31%
<b>Age-group</b>								
10-18y	6 (100%)	60%-99%	5 (83%)	43%-96%	5 (83%)	44%-69%	0 (0%)	-
19-39y	19 (83%)	63%-93%	17 (74%)	53%-87%	17 (74%)	53%-87%	3 (13%)	4%-32%
40-59y	24 (67%)	50%-79%	25 (69%)	53%-82%	23 (64%)	47%-77%	8 (22%)	11%-38%
60+y	14 (67%)	45%-83%	14 (67%)	45%-82%	14 (67%)	45%-82%	6 (29%)	13%-49%
<b>Residency</b>								
Urban	8 (53%)	30%-75%	11 (73%)	48%-89%	12 (80%)	54%-93%	4 (27%)	10%-52%
Rural	55 (77%)	67%-85%	50 (70%)	59%-79%	47 (66%)	54%-76%	13 (18%)	11%-28%

In Table 3 are shown the proportions of chronic (over 1 year persistence since diagnoses) and sub-acute cases (3-12 months persistence since diagnoses) of brucellosis. There are in total 18.6% of cases or almost 1 in 5 cases which present persistence of clinical signs and other complications after at least 3 months from the moment of the diagnoses. Almost 7% of the cases are classified as full chronic cases, with clinical signs or complications persisting after 1 year of diagnoses. No significant differences or relative tendencies were found between age, sex and residency categories.

Table 3. Chronic and sub-acute cases of brucellosis

	Chronic		Sub-acute		Total chronic + sub-acute		Total
	Cases (%)	IC 95%	Cases (%)	IC 95%	Cases (%)	IC 95%	Cases (%)
Males	5 (7.5%)	3.2%-16.3%	8 (11.6%)	6.2%-21.8%	13 (19.4%)	12%-30%	67 (100%)
Females	1 (5.3%)	0.9%-24.6%	2 (11.9%)	2.9%-31.4%	3 (15.8%)	6%-37%	19 (100%)
Total	6 (6.9%)	3.2%-14.4%	10 (11.6%)	6.4%-20.1%	16 (18.6%)	11.8%-28.1%	86 (100%)

The overwhelming majority of brucellosis patients or 75.6% of all cases in Gjirokastra regional hospital during the last 6 years under study have been treated with a combination of doxycycline and ceftriaxone antibiotic regime. 16.2% of patients have been treated with the combination of doxycycline in conjunction with another antibiotic (streptomycin 4.6%, or gentamycin 8.1%, or rifampicin 3.5%). In very few patients either monotherapy (4.6%) or tritherapy (3.5%) have been applied. Only 2 cases have not received doxycycline as a part of their standard treatment regime for brucellosis (Table 4).

Table 4. Treatment of brucellosis

Treatment regime	Monotherapy		Bitherapy		Tritherapy		Total	
	cases	%	cases	%	cases	%	cases	%
Doxycycline	2	2.3%						
Ceftriaxone	2	2.3%						
Doxycycline + Streptomycin			4	4.6%				
Doxycycline + Gentamycin			7	8.1%				

Doxycycline Rifampicin	+		3	3.5%				
Doxycycline Ceftriaxone	+		65	75.6%				
Doxycycline +Streptomycin+ Ceftriaxone					1	1.2%		
Doxycycline +Gentamycin+ Ceftriaxone					2	2.3%		
Total		4	4.7%	79	91.9%	3	3.5%	100%

## Discussion

In this work we describe some clinical and treatment characteristics in the totality of brucellosis patients hospitalized in the regional hospital of Gjirokastra during the last 6 years.

The hospitalized brucellosis patients under study don't represent all cases of the human infections in the region during the same period as some cases may have experienced few or no symptoms (8) and some may have been treated at home. Nonetheless the overwhelming dominance of male cases in the sample most likely mirror the much higher level of risk of brucellosis infection among males in community. This profile can be explained by gender differences in professional exposure to manipulation with livestock products (14). This is further confirmed by the higher proportion of brucellosis patients of rural residency.

The profile of clinical signs observed is similar with that found in most of literature covering clinical human brucellosis (15,16). Fever, joint pain, increased sweating were the most commonly reported symptoms followed by weakness and muscle pain. In young people, there is a systematic tendency of a relatively more frequent presence of high fever, increased sweating and arthralgia. This profile is found also elsewhere in young patients and children (17,18). Some clinical signs such as lumbalgia, were found systematically more often among older patients compared to younger ones. Arthralgia in females seemed to be more common than fever or sweat, compared to males. Similar profile of symptoms is reported in a systematic review (19). Because of the size of our study sample, it has proven impossible to show statistical significance in differences observed. Other studies in larger samples, or in a more extended time span, would be advisable in the future to confirm some of the trends we report in this work.

Brucellosis can get chronicized in a minority of patients with sick individuals experiencing persistence of symptoms for more than 1 year. Such patients are defined as having chronic brucellosis. There are no objective laboratory methods to confirm the presence of chronic disease and the most common definition is based on the time span of the illness, the return of the symptoms and silent organ complications. In our study we found that in total almost 1 in 5 cases presented with persistence of clinical signs and other complications after at least 3 months from the moment of the diagnosis. These cases could be considered as sub-acute and chronic brucellosis. Almost 7% of the cases were classified as full chronic cases, with clinical signs or complications persisting after 1 year of diagnoses. While the proportion of sub-acute patients is relatively lower than that reported by some other studies in specialized literature (6) the proportion of those with symptoms persisting for more than one year is slightly higher than expected (6,13). We found no significant differences or relative tendencies in chronicization risk between age, sex and residency categories. Often chronic patients suffer delays in both diagnosis and treatment (20). The prognosis is poorer in people who develop organ changes or complications such as heart damage, neurological, or genitourinary problems caused by chronic *Brucella* infection.

The goal of medical therapy in brucellosis is to control the disease as quickly as possible in order to prevent chronicization and complications. The drug of choice is doxycycline which is used in conjunction with either streptomycin, rifampin, gentamicin, or sulfamethoxazole / trimethoprim (8). The use of doxycycline as the drug of choice for treating brucellosis is confirmed in our study, as doxycycline is not reported only in two patients out of a total of 86 during 6 years. In those two cases the doxycycline might have been avoided because of the young age of patients (8). On the other hand, the combination of doxycycline with ceftriaxone instead of other recommended antibiotics is striking. More than 75% of patients have been treated with this biotherapy. The observed massive use of a cephalosporin in treatment of brucellosis may reflect a larger problem related to population awareness, health provider attitudes and patient's behaviour concerning antibiotic use in Albania (21,22). While the utilisation of ceftriaxone may be effective in treatment of the acute brucellosis, it is recommended only in complicated cases (23) and its massive application can't be clinically justified.

The results of this study may assist any interventions to improve brucellosis case management at hospital or primary health care level as well as national measures at a larger scale for control of the disease.



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