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Original Research

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# Respiratory System Involvement in Brucellosis

## The Results of the Kardelen Study

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***Background:*** **Pulmonary involvement is a rare complication of brucellosis. We describe the largest series to date, to our knowledge, of patients with pulmonary brucellosis.**
***Methods:*** **This 10-year, retrospective, descriptive study involved 27 centers in Turkey, including all patients with brucellosis with confirmed respiratory system involvement.**
***Results:*** **Of 133 patients (67 men), 123 (92.5%) had acute infection (defined as < 2 months), with an overall mean ± SD duration of symptoms of 33.9 ± 8.5 days. The radiologic pattern of pulmonary disease was consolidation/lobar pneumonia in 91 patients (68.4%) and pleural effusion in 41 patients (30.8%), including 30 (22.5%) with both. Moreover, 23 patients (17.3%) had bronchitis (one with coexistent pneumonia), and 10 (7.5%) had nodular lung lesions (one with coexistent pneumonia and effusion). Blood culture results were positive in 56 of 119 patients, and all other cases were serologically confirmed. None of 60 sputum specimens and two of 19 pleural fluid samples (10.5%) yielded positive culture results for brucellosis. Other features of brucellosis, such as osteoarticular complications, were detected in 61 patients (45.9%); 59 (44.4%) had raised liver transaminase levels, and 59 (44.4%) had thrombocytopenia. Fifteen patients (11.3%) required management in an ICU for an average of 3.8 ± 2.2 days. All patients responded to standard combination antimicrobial therapy for brucellosis with no deaths, although treatment regimens required modification in seven patients.**
***Conclusions:*** **Brucellosis with pulmonary involvement is rare but has a good prognosis following treatment with appropriate antibiotics. Many clues in the exposure history, presenting clinical features, and baseline blood tests should alert the clinician to consider brucellosis.**
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**Abbreviations:** CAP = community-acquired pneumonia; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LOS = length of stay; STA = standard tube agglutination

Pulmonary involvement is reported in up to 20% of patients with brucellosis, manifesting as a dry cough with no other respiratory signs.[1] The pathogenesis of this condition is not understood. Objective features of respiratory involvement are only present in about 1% of patients with brucellosis.[1-4] Interstitial pneumonia, lobar pneumonia, bronchitis, and pleural effusion are the most common manifestations reported.[5-7] Granuloma formation and solitary nodules in the parenchyma, hilar lymphadenopathy, empyema, and abscesses have also been observed.[7-10] Although brucellae can be transmitted through the air,[11] the association between the development of pneumonia and airborne transmission is weak.[12] In areas endemic for brucellosis, the pulmonary form of the disease is reported to be one of the sporadic causes of community-acquired pneumonia (CAP).[13] Very few published case series have described the pulmonary manifestations of brucellosis, the largest of which included 37 patients.[14] We combined data from many centers in a country where brucellosis is endemic to form, to our knowledge, the largest-ever reported case series of the clinical, diagnostic, and therapeutic implications of pulmonary involvement in brucellosis.

## Materials and Methods

### *Study Design, Patients, and Participating Centers*

This retrospective, multicenter clinical study was performed between 2002 and 2012 and included all patients hospitalized with objective respiratory system involvement due to brucellosis at 27 participant centers in Turkey (the Kardelen study). The primary aims were to describe the presenting epidemiologic and clinical features, the laboratory and radiologic findings, and the outcomes of treatment of patients with respiratory involvement. A standard form was used to collect individual patient data from each center. No control groups were included, and standardized data could not be collated on the incidence of all brucellosis cases concurrently diagnosed or treated at the participating centers. Institutional review board approval was obtained from Haydarpasa Numune Training and Research Hospital (HNEAH-KAEK/KK/17).

The study inclusion criteria[14] were as follows: (1) presence of symptoms or physical findings related to respiratory systems, (2) confirmation of respiratory involvement by radiologic methods (except for bronchitis), and (3) diagnosis of brucellosis by direct (culture) or indirect (serology, polymerase chain reaction) methods. Standard tube agglutination (STA) test titers of 1:160 and higher were considered positive for brucellosis. Exclusion criteria were as follows: (1) positive blood and sputum culture results for causative agents other than *Brucella* species; (2) positive acid-fast staining or culture results for *Mycobacterium tuberculosis*; (3) positive purified protein derivative test results (with Bacillus Calmette-Guérin vaccination, > 15 mm; without Bacillus Calmette-Guérin vaccination, > 10 mm; for people with immunosuppression, > 5 mm); (4) positive serology for *Mycoplasma* species, *Chlamydophila pneumoniae*, *Coxiella burnetii*, or *Legionella* species; (5) positive sputum or pleural fluid cytologic findings favoring malignancy; and (6) presence of any other condition that can explain the pulmonary disease.

### *Clinical and Laboratory Analyses and Follow-up Period*

At a minimum, patients were evaluated on admission, daily during their hospitalization, and 6 months after discharge from the hospital. Response to treatment and adverse drug events were monitored through clinical and laboratory data. Combination antibiotic therapy was continued until clinical improvement and resolution by either chest radiograph or thoracic CT imaging. In addition, antibiotics were continued until resolution of all other foci of brucellosis. Antibiotic treatment was modified if therapeutic failure or adverse drug effects were observed.

### *Microbiologic and Serologic Investigations*

Blood culture specimens were cultured by automatic systems in different centers, mainly by the BACTEC 9240 system (Becton Dickinson and Company). Blood samples were inoculated into the BACTEC system for 14 days. Clinical specimens other than blood, including cerebrospinal fluid, synovial fluid, and sputum, were inoculated onto sheep blood agar and chocolate agar. For agglutination tests, *Brucella abortus* S99 antigen obtained from Pendik Animal Diseases Research Institute (Istanbul, Turkey) was used. The three methods used for serologic analysis were Rose Bengal test (slide agglutination method), Wright STA test (microdilution method), and Coombs test (a microdilution method used to detect nonagglutinating antibodies with human antiglobulin).

### *Definitions*

Brucellosis was defined as clinical findings in accordance with the disease, positive Rose Bengal or Wright STA test results at titers of 1:160 or higher, or isolation of *Brucella* species from body fluids.[15] According to the duration of symptoms, brucellosis was classified as acute (< 8 weeks), subacute (8-52 weeks), and chronic (> 52 weeks).[16] Therapeutic failure was defined as the persistence or deterioration of symptoms and signs related to respiratory system involvement in patients with brucellosis. Relapse was defined as the reappearance of clinical signs and symptoms with or without a positive culture finding.[17]

### *Data Collection and Statistical Methods*

The following patient details were collected from each participating center and entered into a computer database: (1) demographic and epidemiologic data, including age, sex, and risk factors for brucellosis; (2) clinical and laboratory data, including duration of disease, symptoms and signs, coexistent foci of brucellosis other than the pulmonary system, comorbid diseases, routine and other diagnostic laboratory test results, radiologic findings, and focal complications; (3) treatment data, including drug combinations used, duration of treatments, and treatment failures for each drug combination and modification; and (4) outcome data, including cure, disease relapse or death, and length of stay (LOS) in the hospital.

Statistical analysis was performed with SPSS for Windows, version16.5 (IBM Corporation). Descriptive statistics were presented as frequency and percent or mean ± SD and range as appropriate. $\chi^2$ and Fisher exact tests were used to compare categorical variables, and Student *t* and Mann-Whitney *U* tests were used for comparisons of continuous variables. $P < .05$ was considered statistically significant.

## Results

Overall, 133 patients (67 men) with respiratory system involvement were included in this study. Their mean age was 43.3 ± 16.6 years (range, 15-91 years).

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