CHEST

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 associ-ation 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.

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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, version 16.5 (IBM Corporation). Descriptive statistics were presented as frequency and percent or mean ± SD and range as appropriate. χ^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).

Their risk factors for brucellosis were consumption of unpasteurized dairy products (n = 81, 61.9%), raising livestock (n = 23, 17.3%), being a veterinarian or veterinary staff member (n = 2, 1.5%), and family history of brucellosis (n = 1, 0.8%). Twenty-five patients (18.8%) had more than one risk factor.

Clinical Characteristics

Overall, 123 patients (92.5%) had acute disease, eight (6%) had subacute disease, and two (1.5%) had chronic symptoms. Sixteen (12%) had a history of previous brucellosis, which preceded the current admission by 29 ± 3.1 months. The duration of complaints related to respiratory system involvement for all patients was 33.9 ± 8.5 days. Symptoms at the time of admission were fatigue in 116 patients (87.2%), cough in 114 (85.7%), sweating in 106 (79.6%), lack of appetite in 99 (74.4%), arthralgia in 91 (68.4%), dyspnea in 81 (60.9%), back pain in 73 (54.8%), productive sputum in 43 (32.3%), weight loss in 36 (27%), tachycardia in 31 (23.3%), chest pain in six (4.5%), rash in two (1.5%), hemoptysis in one (0.7%), and abdominal pain one (0.7%). Fever (temperature, > 38°C) was detected in all patients, with crackles in 89 (67%), hepatomegaly in 44 (33%), splenomegaly in 21 (16%), cyanosis in three (2.2%), decreased breath sounds in nine (6.7%), intercostal retractions in one (0.7%), and systolic heart murmur in one (0.7%).

Focal brucellar involvement in areas other than the respiratory tract was observed in 73 patients (54.9%). Coexisting osteoarticular complications were detected in 61 patients (45.9%) (spondylodiscitis, 32; arthritis, 25; sacroiliitis, 31). Other forms of coexistent focal disease were observed in 12 patients (hepatitis, five; meningitis, two; endocarditis, two; pericarditis, one; epididymoorchitis, one; uveitis, one).

Underlying pulmonary disorders were present in 13 patients (9.8%) (12 with COPD, one bronchiectasis). Other concomitant conditions were hypertension (n = 12), diabetes mellitus (n = 8), chronic hepatitis C (n = 2), rheumatic valvular heart disease (n = 1), degenerative valvular heart disease (n = 1), chronic renal failure (n = 1), ankylosing spondylitis (n = 1), rheumatoid arthritis (n = 1), polycythemia vera (n = 1), benign prostatic hypertrophy (n = 1), and inguinal hernia (n = 1). One patient used methotrexate and one received anti-tumor necrosis factor-α (adalimumab) as immunosuppressive drugs in the past 3 months, whereas seven patients used inhaled corticosteroids.

Microbiologic Investigations

The results of microbiologic investigations are summarized in Table 1. In 132 patients, at least one serologic test result was positive, Rose Bengal test results were positive in 109 of 131 patients (83.2%), and Wright

Table 1—Results of Microbiologic Investigations for Brucellosis in Patients With Pulmonary Involvement

Test	No. Tested	No. (%) Positive
Rose Bengal	131	109 (83.2)
Wright STA	133	125 (94)
Coombs-STA	51	49 (96.1)
STA (−), Coombs-STA (+)	8	4 (50)
Automated culture results		
Blood culture (automated)	119	56 (47.1)
Bone marrow culture (automated)	13	7 (53.8)
Conventional culture		
Pleural fluid	19	2 (10.5)
Endotracheal aspirate	3	1 (33.3)
Sputum	60	0 (0)

STA = standard tube agglutination.

test results were positive in 125 of 133 (94%) at titers of ≥ 1:160 up to 1:2,560. On the other hand, in 58 of 133 patients (43.6%), 66 clinical specimens yielded positive culture results. Nineteen of these isolates were identified as *Brucella melitensis*, and subtyping was not performed on the remaining 47. *Brucella* species were isolated from only blood in 48 patients, from only bone marrow in one, from only a pleural effusion sample in one, from both endotracheal aspirate and bone marrow in one, from both pleural fluid and blood in one, and from both blood and bone marrow in six. Four of the eight patients with negative Wright test results at titers of ≤ 1:80 had seropositive findings on Coombs-STA test at titers of ≥ 1:160). All four patients with negative Coombs-STA test results had positive blood culture findings for *Brucella* species.

Routine Laboratory Analyses

Routine laboratory test results on admission are shown in Table 2. There was leukopenia in 30 patients (22.6%), anemia in 45 (33.8%), thrombocytopenia in 59 (44.4%), and pancytopenia in 17 (12.8%). The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were raised in 87 (65.4%) and 117 patients (87.9%), respectively. Liver transaminase values were higher than the normal levels in 59 patients (44.4%), with mean values increased up to 1.5-fold (data not shown).

Pleural fluid analyses were performed in 11 patients. Neutrophilic predominance was seen in one, whereas lymphomonocytic predominance was detected in 10. In one patient, the cell count was > 2,000/mm³, and in the other 10, it was < 100/mm³. Pleural fluid was reported as exudate in three and transudate in eight patients.

Chest Radiographs and CT Images

Findings from chest radiography and thoracic CT imaging in patients with brucellosis with pulmonary

Table 2—Laboratory Findings of Brucellosis in Patients With Pulmonary Involvement on Admission (N = 133)

Test	Mean ± SD	Range	Normal
WBC, × 10³/L	6,329 ± 3,220	1,050-27,930	4,000-11,000
Hemoglobin, g/dL	12.3 ± 2.1	6-16.8	14-18 (male), 12-16 (female)
Platelet, × 10³/L	229,875 ± 121,963	27,000-610,000	150,000-450,000
Erythrocyte sedimentation rate, mm/h	36.5 ± 25.2	1-119	≤ 15 (male), ≤ 20 (female)
C-reactive protein, mg/L	8.6 ± 7.2	0.1-31.8	0-8
Alanine aminotransferase, IU/L	47.9 ± 34.1	8-166	17-63
Aspartate aminotransferase, IU/L	50.5 ± 41.9	11-254	15-41
Alkaline phosphatase, IU/L (n = 109)	138 ± 157	10-1,497	41-133
Creatinine phosphokinase, IU/L (n = 92)	122 ± 144	14-888	60-400
Lactate dehydrogenase, IU/L (n = 89)	376 ± 274	69-1,253	140-280
Creatinine, IU/L	0.85 ± 0.27	0.2-2.1	0.7-1.2

involvement are summarized in Table 3. Ninety-one patients (68.4%) had pneumonia; 41 (30.8%) pleural effusion (30 of whom had coexistent pneumonia [22.5%]); 23 (17.3%) bronchitis (one of whom had coexistent pneumonia); and 10 (7.5%) nodular lung lesions, which were bilateral in three patients (one had coexistent pneumonia and effusion). Five of the patients with nodular lung lesions had very small (millimeters) nodules, one had a 1-cm nodule, and the remaining four had unreported sizes. Thus, when the 91 patients with pneumonia were excluded, 22 had bronchitis, 11 had pleural effusion, and nine had pulmonary nodules. Pulmonary embolism was detected in two patients with coexistent pneumonia, bronchiolitis in one patient, and ARDS in one patient with lung nodules.

Treatment Issues

Treatment and outcome data are summarized in Table 4. Appropriate antibiotic treatment of brucellosis was started 3.6 ± 4.4 days after hospitalization. Overall, antibiotics were modified in 11 patients for side effects in seven and following therapeutic failure in four.

For therapeutic failures, fluoroquinolones (three patients) or streptomycin (one patient) were added to the treatment regimen on either the 10th, 22nd, 35th, or 89th days of therapy. In two patients, either complaints related to the respiratory system did not resolve or inflammatory markers (CRP, ESR) did not normalize. In one patient, fever was not controlled with antibiotics, and high levels of ESR and CRP persisted. Finally, in one patient, radiologic findings progressed, fever could not be controlled, and respiratory status deteriorated. Three relapses were observed between 30 and 60 days after stopping antibiotic therapy.

Outcomes for patients with pulmonary involvement as the only focal brucellar disease were compared with those with coexistent disease or other focal forms of brucellosis (Table 5). When patients with pneumonia only (n = 60; one patient with coexistent bronchitis was excluded) and those with coexistent pleural involvement (n = 30) were compared, the mean treatment duration was similar (50.9 days vs 51.1 days, respectively; P = .98). However, the mean LOS in patients with pneumonia only (13.2 days) was significantly lower than that of patients with coexistent pleural disease (18.8 days; P = .01).

Status of Critical Cases

Overall, 33 patients (24.8%) were given oxygen by nasal cannula. Fifteen (11.3%) required admission to the ICU, of whom 11 (73.3%) had bilateral pulmonary

Table 3—Chest Radiograph and Thoracic CT Imaging Findings

Radiologic Finding	No. Patients	Chest Radiograph (n = 133)	Thoracic CT Imaging (n = 92)
Consolidation	84	77 (57.9)	58 (63)
Interstitial or patchy infiltration	32	29 (21.8)	27 (29.3)
Parenchymal nodules	10	9 (6.8)	10 (10.9)
Abscess	1	1 (0.8)	1 (1.1)
Cavity	1	1 (0.8)	1 (1.1)
Pleural effusion	44	38 (28.6)	38 (41.3)
Bilateral	27	15 (11.3)	25 (27.2)
Unilateral	17	23 (17.3)	12 (13)
Localization			
Limited to one to two lobes	74	73 (54.9)	43 (46.7)
More than two lobes	17	14 (10.5)	14 (15.2)
Bilateral infiltration	46	38 (28.6)	35 (38)

Data are presented as No. (%).

Antibiotic Combination	No. Patients	Duration, d	LOS, d	Failure	Relapse	Negative Outcome
Doxy + Rif	82	44.4 ± 10.4 (28-90)	12.1 ± 5.8 (3-30)	0	1 (1.2)	2 (2.4)
Doxy + Rif + Str	16	55.9 ± 35.1 (42-180)	15.6 ± 9.1 (6-30)	2 (12.5)	1 (6.2)	3 (18.8)
Doxy + Str	10	42.3 ± 0.9 (42-45)	19 ± 11.3 (6-42)	0 (0)	0 (0)	0 (0)
Doxy + Rif + Str + Cfxn	8	39.4 ± 6 (28-45)	13.6 ± 3.4 (7-17)	0 (0)	0 (0)	0 (0)
Doxy + Rif + Cfxn + Fq[a]	7	82.3 ± 66.7 (42-180)	25.6 ± 13.6 (15-50)	0 (0)	0 (0)	0 (0)
Doxy + Rif + Fq	3	80 ± 48.2 (45-135)	18.3 ± 3.8 (14-21)	1 (33.3)	1 (33.3)	1 (33.3)
Doxy + Rif + TMP-SXT	2	58.5 ± 23.5 (42-75)	33 ± 26.8 (14-52)	0 (0)	0 (0)	0 (0)
Other[b]	5	113.8 ± 79.8 (42-215)	26.8 ± 14.5 (15-51)	1 (20)	0 (0)	1 (20)
Total	133	50.9 ± 30.1 (28-215)	15.3 ± 9.4 (3-52)	4 (3)	3 (2.3)	7 (5.3)

Data are presented as mean ± SD (range) or No. (%). Cfxn = ceftriaxone; Doxy = doxycycline; Fq = fluoroquinolone; Gm = gentamycin; LOS = length of stay; Rif = rifampin; Str = streptomycin; TMP-SXT = trimethoprim/sulfamethoxazole.
[a]Ciprofloxacin or levofloxacin or ofloxacin or moxifloxacin.
[b]Doxy + Cfxn + Str; Doxy + Cfxn + Gm; Doxy + Gm; Doxy + Rif + Gm; Rif + Fq + Gm.

involvement and one (6.6%) had unilateral involvement of more than two lobes. Invasive mechanical ventilation was required for two patients, and one patient with septic shock required vasopressors. Hypotension was observed in five patients. The mean LOS in the ICU was 3.8 ± 2.2 days, and the mean total LOS in the hospital for these patients was 21.4 ± 1.3 days.

Discussion

To our knowledge, this series is the largest reported of patients with respiratory involvement due to brucellosis. When isolates were confirmed at the species level, all were due to *B melitensis*, the predominant species in our region. Risk factors for acquiring infection were typical of those reported.[18,19] Men and women were equally affected, with age ranges expected in a brucellosis-exposed community. Unfortunately, we could not collect accurate denominator data on the incidence of pulmonary complications, but data for these 133 patients were collected over 1 decade in 27 centers in an endemic country, and it is likely that the rate is similar to the 1% previously suggested.[1,4,19,20]

The exact mechanism of pulmonary involvement is unknown. The most probable routes of transmission

are inhalation of contaminated aerosols and hematogenous spread. Sand and airborne dust have the potential to carry *Brucella* species.[21] Transmission by inhalation of organisms is well recognized in laboratory-acquired cases[22] and in abattoir workers,[23] but lung involvement is not as frequent as might be expected because only one of eight workers who acquired brucellosis in an airborne laboratory outbreak had pneumonia.[12] Respiratory involvement is rare in abattoir-associated outbreaks.[1] Nevertheless, human-to-human transmission of brucellosis through the aerosol route has been hypothesized to occur under crowded conditions, as in 19th century sailing ships.[24] The efficiency of airborne transmission is such that a bioterrorism attack with brucellae would likely be delivered by the aerosol route.[25] Most of the present patients had a history of consuming unpasteurized dairy products, the most likely route of transmission. Brucellae are said to infect traumatized tissues frequently.[26] In this uncontrolled study, one-tenth of the patients had coexistent pulmonary disorders.

Most of the patients had acute presentations, with respiratory symptoms for up to 1 month before hospital admission, which is longer than for most other CAPs but shorter than other chronic complications of brucellosis.[27] Clinical features such as cough, dyspnea, productive sputum, pleuritic chest pain, fever, and crackles were similar to those in other lower respiratory tract infections.[28,29] Hemoptysis was rare. Similarly, radiologic examination did not reveal specific findings in brucellosis with pulmonary involvement. Consolidation, hilar lymphadenopathy, pleural effusion, pneumothorax, abscess, and parenchymal nodules have all been documented.[7,10,14,30-32] Pappas et al[14] reported interstitial changes to be the most significant radiologic finding followed by lobar pneumonia. In the present series, consolidation was seen in two-thirds of the patients, and a pleural effusion was observed in one-third of patients in whom it was bilateral in two-thirds. Interstitial or patchy infiltration was noted in one-fifth of patients.

Table 5—*Comparison of Respiratory Brucellosis in Patients Without Other Coexistent Focal Disease (Group 1) and With Other Involved Sites (Group 2)*

Variable	Group 1 (n = 61)	Group 2 (n = 72)	P Value
Duration, d	42.6 ± 9.9 (28-90)	51.6 ± 31 (32-180)	.044[a]
LOS, d	13.8 ± 7 (42-180)	15 ± 9.5 (6-30)	.039[a]
Failure	1 (1.6)	3 (4.2)	.624
Relapse	1 (1.6)	2 (2.8)	1
Fatal outcome	1 (1.6)	0 (0)	.459
Negative outcome	2 (3.2)	5 (6.9)	.452

Data are presented as mean ± SD (range) or No. (%). See Table 4 legend for expansion of abbreviation.
[a]Significant at P < .05.

Consequently, the radiologic findings and clinical presentation can easily be confused with other causes of CAP.

Pulmonary nodules, frequently small (millimeters), were seen in a small proportion of patients (7.5%). Pulmonary brucellosis must always be included in the differential diagnosis of TB and vice versa, especially when miliary mottling, hemoptysis, or prolonged respiratory symptoms are present.[30,33] In addition, the present series confirms previous observations that characteristics of the pleural effusion in brucellosis mimic those of TB, usually being exudative with pleural fluid lymphocytosis.[33] We did not use pleural fluid adenosine deaminase because this does not help to differentiate between brucellosis and TB.[33]

Our experience reveals other bedside clues to help the clinician to differentiate respiratory brucellosis from TB or other causes of CAP. Apart from a history of living in or visiting an endemic area, most patients had a history of consuming unpasteurized milk products and possibly having a past or family history of brucellosis. Almost one-half of the patients had significant osteoarticular disease, and this is unusual in CAP and TB.

General laboratory findings mirror those expected in brucellosis.[18,19] Mild elevations of ESR and CRP levels were common but unhelpful. Mild to moderate hepatitis is common in brucellosis.[18,19] Anemia, leukopenia, leukocytosis, thrombocytopenia, thrombocytosis, and pancytopenia may all occur during the course of brucellosis.[2,3,18,19] The combination of raised transaminase levels and thrombocytopenia is unusual in patients with pulmonary TB,[34] and this should alert the clinician to the possibility of brucellosis.

All but one patient had confirmed disease by one of a panel of brucellosis serologic tests, with positive blood culture results in 47% and a better culture yield of 54% from bone marrow samples from difficult-to-diagnose cases. These findings are all typical of brucellosis.[26,35,36] In this study, the sensitivity of Rose Bengal test was 83% and 94% for Wright agglutination test. Blood serology is known to lead to a diagnosis in a significant portion of patients with focal brucellar disease other than in the respiratory system,[26,35] and the present data agree. Of interest, one-half of the patients with negative Wright test findings had positive Coombs-STA results. In the literature, reports favor the use of Coombs-STA or immunocapture enzyme-linked immunosorbent assay in which the microwell is coated with antibodies against human IgG, IgM, and IgA.[37,38] However, respiratory culture yield was very low, with none of 60 sputum samples and only 10% of pleural effusion samples showing positive results. Only one patient had positive results on pleural fluid culture alone. Similar results were reported in the Pappas et al[14] series from Greece. These findings also argue against

substantial direct pulmonary invasion by *Brucella* organisms, which must cause disease indirectly. On the other hand, automated culture systems are known to be much more efficient than conventional cultures for body fluids other than those of the respiratory system,[35,39] and the use of these systems can increase the yield. Use of molecular diagnostic tools may give a better yield.[40] The practical message is that clinicians will not diagnose respiratory brucellosis unless they identify epidemiologic risk and clinical features of brucellosis and then request specific serologic and culture methods to confirm the diagnosis.

For CAP, typically 2% to 20% of patients are admitted to the ICU.[41,42] One-fourth of the present patients with respiratory involvement due to brucellosis required supplementary oxygen through nasal cannula, and 10% had severe pulmonary disease that required ICU admission for an average of 4 days. These data are similar to other forms of community-acquired lower respiratory infections. However, none of the patients died, and pulmonary brucellosis had a favorable prognosis compared with other forms of CAP, where mortality rates can be as high as 20% to 50% for those who require ICU care.[43,44]

The patients were treated with combination antimicrobial regimens for 6 weeks, which is the standard of care for uncomplicated brucellosis when a TB diagnosis has been excluded.[19,45] Clinical outcomes were excellent, with only 5% experiencing problems irrespective of the pattern of respiratory involvement. Hospital LOS was slightly prolonged in those with pleural effusions or with other focal features of brucellosis or concomitant disease.

This study has a number of limitations. It includes retrospective data collected from many centers over 10 years; thus, it was not possible to standardize laboratory methodology or clinical management. Nevertheless, the background epidemiologic, clinical, and laboratory findings are in keeping with those expected in the region. We were unable to provide denominator data to evaluate the frequency of respiratory complaints in brucellosis because of incompleteness of hospital databases, which rarely include patients managed as outpatients. As a result, this series only includes patients admitted to the hospital with proven respiratory involvement and excludes the 20% of patients with brucellosis who had dry cough as an unexplained presenting symptom. The strength of the study lies in its inclusion of all patients from many centers, so the frequency of different types of presentation is representative, and results can be generalized to other settings.

In summary, this study is the largest published series, to our knowledge, of patients with pulmonary complications of brucellosis. The majority of patients presented with lobar pneumonia, with or without pleural effusions, that was radiologically similar to those seen

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in other types of CAP. A much smaller proportion had nodular or parenchymal changes that mimic TB. Pleural fluid examination revealed similar changes to those in TB. Diagnosis of both these infections requires specific laboratory tests, and differentiation between TB and brucellosis is essential because the combination regimens used to treat these diseases may contain similar antimicrobial agents (rifampin, streptomycin) and need to be tailored.

Clinicians should be alert to the possibility of brucellosis being the cause of respiratory problems, especially in those suspected of having TB. Clues include a history of residence in or travel to an endemic area, consumption of unpasteurized milk products, and a past or family history of brucellosis. Respiratory symptoms often have been present for 1 month before admission for *Brucella* pneumonia, and almost one-half of the patients have significant concurrent rheumatologic symptoms. In baseline laboratory investigation, neutrophilia is uncommon, but many patients have mildly raised transaminase levels and thrombocytopenia. All these clues should prompt the clinician to request the specific serologic and culture tests required for the diagnosis of a condition with excellent outcomes following specific combination antimicrobial therapy, which typically includes a 6-week course of doxycycline with rifampin or an aminoglycoside.

Additional information: The e-Appendix can be found in the "Supplemental Materials" area of the online article.

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