



Case report

Ceftriaxone use in brucellosis: A case series

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ABSTRACT

Background: Brucellosis is a zoonotic disease caused by *Brucella* spp. It can be either uncomplicated or complicated when it disseminates to other organs. Treatment for brucellosis involves a combination of at least two antibiotics, or more in complicated brucellosis. Limited data exist on the use of ceftriaxone in the clinical setting. Therefore, we present patient cases in which ceftriaxone was used in brucellosis treatment regimen.

Methods: Patients with documented brucellosis from January 2008 to December 2018 were evaluated for the use of ceftriaxone for treatment in King Abdulaziz Univeristy Hospital, Jeddah, Saudi Arabia. Patients' data were evaluated retrospectively and are described.

Results: Out of 94 treated brucellosis patients, six patients received ceftriaxone 2 g IV every 12 h for therapy for varied durations. Four had neurobrucellosis, one had *Brucella* epididymo-orchitis and one had uncomplicated brucellosis. All six patients experienced clinical cure, though one neurobrucellosis patient had complications and one had ceftriaxone stopped after one week of therapy due to presumed antibiotic-induced fever.

Conclusion: Ceftriaxone represents a reasonable option for the treatment of complicated brucellosis when added to the initial regimen at a dose of 2 g IV every 12 h.

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Introduction

Brucellosis is a widespread zoonotic disease caused by various *Brucella* species [1]. The four most common causes of human brucellosis in order of frequency are *B. melitensis*, *B. abortus*, *B. suis* and *B. canis* [2]. The disease is usually transmitted through contact with infected animals or contaminated animal products. Animals that are most commonly infected include sheep, cows, goats, camels, pigs and dogs, among others. Eating or drinking unpasteurized raw dairy products is the most common mode of transmission of the infection [1,2]. Brucellosis remains an endemic disease that is common in the Middle East, Turkey, Mexico, South America, central Asia and the Asia-Pacific region [3,4].

Common clinical features of brucellosis include acute or insidious onset of symptoms, associated with continued, intermittent, or irregular fever with variable duration, associated with profuse sweating, fatigue, anorexia, weight loss, headache, arthralgia and generalized aching [1]. *Brucella* spp. can disseminate

to certain organs resulting in complicated brucellosis. The most commonly affected organs are the central nervous system (causing neurobrucellosis), spine (causing spondylodiscitis), heart (causing endocarditis) and the testicles (causing orchitis) [1,2]. Neurobrucellosis and *Brucella* endocarditis are the most common causes of death due to *Brucella* infection [1].

Administration of effective antibiotics for an adequate period of time is crucial in the treatment of all forms of human brucellosis. Uncomplicated cases in adults and children of eight years and older are usually treated with doxycycline 100 mg twice a day for six weeks in combination with streptomycin 1 g (or any other aminoglycoside, such as amikacin or gentamicin) daily for two to three weeks. Alternatively, rifampin (rifampin) 15 mg/kg/day (600–900 mg) daily for six weeks may replace streptomycin in addition to doxycycline to provide an easier outpatient oral regimen [1,2,5]. Other recommended regimens include trimethoprim/sulfamethoxazole (TMP/SMX) or ciprofloxacin plus doxycycline or rifampin [1,2,5]. Similar regimens (excluding fluoroquinolones) are also used in pregnant women, neonates and children under eight [1]. Management of complicated brucellosis involves the use of regimens comprised more than two of the aforementioned antibiotics in contrast to uncomplicated brucellosis which is usually treated with two agents [1,5]. Ceftriaxone is another antibiotic that is active against *B. melitensis* *in vitro*; however there are no specific recommendations regarding its use clinically due to

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limited clinical data [6,7]. Current treatment with ceftriaxone is based on small case series and anecdotal reports since no randomized controlled trials have been done to compare it with treatment regimens excluding it. Reports published in the literature showed positive outcomes when ceftriaxone was added to the treatment regimen [8–13]. Furthermore, as a β -lactam antibiotic, ceftriaxone is generally considered safe with a very mild adverse reaction profile [14].

In this cases series, we report six brucellosis cases (four neurobrucellosis, one *Brucella* epididymo-orchitis and one uncomplicated brucellosis) that involved the use of ceftriaxone along with other antibiotics active against the pathogen in order to provide additional evidence on the usefulness of ceftriaxone for the management of this disease. Medical records of adult patients who had positive *Brucella* culture or positive serology with antibody titer of $\geq 1:640$ (or lower but had symptoms consistent with brucellosis) and received antibiotic therapy for the infection between January 2008 and December 2018 at King Abdulaziz University Hospital, Jeddah, Saudi Arabia were reviewed. For the serological diagnosis of brucellosis, an antibody titer cutoff value of at least 1:640 is considered at our institution that is in a country endemic for brucellosis. Out of 94 patients with documented brucellosis, six patients received ceftriaxone as part of the treatment regimen. The study protocol was approved by the Biomedical Research Ethics Unit, Faculty of Medicine, King Abdulaziz University.

Patient cases

Case 1

A 25-year-old man, previously healthy, was initially admitted due to slowly progressive headache with blurry vision and fever for nine months. The patient recalls ingesting raw camel milk, which is a major risk factor for brucellosis. There was no previous contact with a tuberculosis case. The headache worsened one week before his admission and the patient lost vision in the left eye. His vital signs and cognitive function were normal. Pupils were reactive, but the patient was barely seeing the flash light with his left eye. Ophthalmologic examination revealed an atrophic optic disc mainly with decreased visual acuity bilaterally. Extraocular muscles were intact. The remaining neurological examination was unremarkable.

His diagnostic work up showed total white blood cell (WBC) count of 5.61×10^9 cells/mm³ and a C-reactive protein (CRP) level of 3.76 mg/L.

His cerebrospinal fluid (CSF) acid fast bacilli (AFB) stain and *Mycobacterium tuberculosis* polymerase chain reaction (MTB-PCR) were both negative. Blood and CSF cultures were positive for *Brucella* spp. His serum serological test was positive for *B. melitensis* and *B. abortus*. Antibody titers were 1:640 for both strains, just at the cutoff level for the serological diagnosis of the infection. CSF analysis showed elevated WBC count (170 cells/mm³ with 34.9% lymphocytes) and decreased glucose level (34.2 mg/dL). Serum glucose level at that time was 99 mg/dL. CSF protein level was 1.5 g/L while red blood cell (RBC) count was 7 cells/mm³. A magnetic resonance imaging (MRI) of his brain showed multiple, bilateral small dural-based nodular enhancements in both upper frontal lobes (Image 1). The patient was diagnosed with neurobrucellosis. Unfortunately, the patient has completely lost his vision in the left eye with weakened vision in the right eye because of a late presentation and delayed diagnosis. As such, the patient was immediately started on ceftriaxone 2 g intravenously (IV) every 12 h, doxycycline 100 mg orally every 12 h and rifampin 900 mg orally once daily for six weeks along with amikacin 400 mg IV every 12 h for the first three weeks. Three weeks after treatment was initiated, both antibody titers remained at 1:640, which was expected as *Brucella* antibodies may persist for months after conclusion of therapy [15]. His repeated blood and CSF cultures returned negative a few days after treatment. A repeated MRI of the brain showed interval decrease in the number of the previously reported bilateral frontal leptomenigeal enhancing foci. However, small residual abnormal enhancing foci were still noted. Fortunately, no interval development of new lesions was seen (Image 2).

Upon completion of the IV regimen (amikacin and ceftriaxone), the patient was discharged on oral doxycycline 100 mg every 12 h and rifampin 300 mg every 8 h to be taken for 6 months. In an outpatient follow up visit three months later, the patient's vision on the right side was slightly improving. While *B. melitensis* antibody titer slightly decreased to 1:320, *B. abortus* antibody titer remained at 1:640. Three months later (six months after discharge), a repeated lumbar puncture showed improved CSF analysis with WBC count of 6 cells/mm³, RBC count of 1 cell/mm³, protein level of 0.55 g/L and glucose level of 46.8 mg/dL (serum glucose level was not obtained at the time of this test). *Brucella* antibody titer in the serum declined from 1:640 to 1:40 for both strains. At this visit, the decision was made to extend the treatment to 3–6 more months to ensure full recovery. Three months later, a repeated brain MRI showed no more meningeal enhancement and CSF analysis was normal; therefore, antibiotic treatment for brucellosis was stopped.

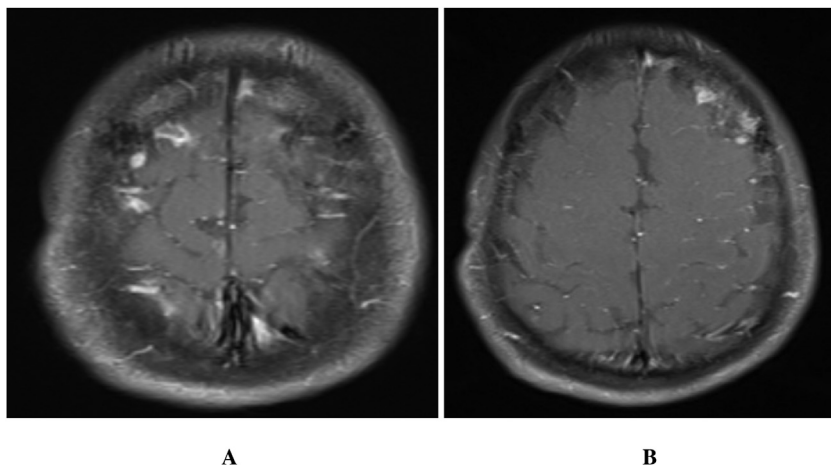


Image 1. Brain magnetic resonance imaging of patient case 1 at baseline on T1 post contrast cuts showing multiple enhancing dural based lesions in both upper frontal lobes at different levels.

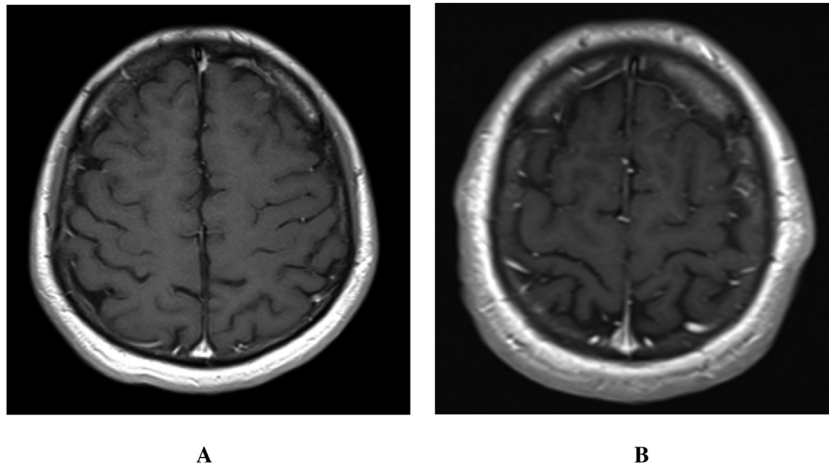


Image 2. Brain magnetic resonance imaging of patient case 1 after three weeks of treatment.

Case 2

A 54-year-old woman, known case of type 2 diabetes mellitus and hypertension, was admitted to the hospital due to fever, severe neck and back pain, as well as nausea and vomiting for 2 weeks. She admitted drinking a small amount of raw milk several weeks before her presentation. She had no signs of meningitis and her neurological examination was normal. A lumbar puncture revealed no bacterial growth with CSF protein level of 0.7 g/L and glucose level of 126 mg/dL (serum glucose level was 268.2 mg/dL). CSF WBC count was <1 cell/mm³ and RBC count was 8 cells/mm³. AFB stain showed no *Mycobacteria*, and CSF MTB-PCR did not detect *M. tuberculosis*. Urine culture came back negative for any bacterial growth. However, a blood culture was positive for *Brucella* spp. In addition, both *B. melitensis* and *B. abortus* antibody titers in the serum exceeded 1:1280. An abdominal ultrasound was unremarkable. A transthoracic echocardiography followed by a transesophageal echocardiography were both normal. The patient was immediately started on ceftriaxone 2 g IV every 12 h, streptomycin 1 g intramuscularly (IM) once daily, doxycycline 100 mg orally every 12 h and rifampin 300 mg orally every 8 h daily for a total duration of 6 weeks. Her nausea and vomiting were treated with metoclopramide and ondansetron. Her back pain appeared to be due to disc prolapse rather than *Brucella* spondylodiscitis as was concluded from the MRI of her cervical and lumbosacral areas. After the patient completed 12 days of therapy, she was discharged on doxycycline 100 mg orally every 12 h and rifampin 300 mg orally every 8 h for 30 days and to continue her parenteral antibiotics as an outpatient. Upon follow up one month later, both *Brucella* antibody titers declined to 1:1280 in the serum. CRP level was 6.93 mg/L (no level was obtained at baseline). The patient was advised to continue the oral antibiotics for 6 more weeks while streptomycin and ceftriaxone were stopped. Two months later (three months post discharge), CRP level increased to 31 mg/L; nonetheless, antibody titers of *B. melitensis* and *B. abortus* declined to 1:640 and 1:320, respectively. As the patient appeared asymptomatic and clinically well, her antibiotics were stopped; though, she was advised to remain under supervision and to return for follow up in case of a potential relapse.

Case 3

A 31-years-old man who was otherwise healthy presented to the emergency department with high grade fever that persisted for a week but was manageable with acetaminophen (paracetamol). The patient also suffered from headache for three days which he

described as being band-like surrounding his head. He reported regular contact with camels and occasional consumption of their raw milk. Three weeks before presentation, he was on vacation in Turkey where he consumed raw dairy products at a rural farm. He was febrile but his physical examination was normal otherwise. Lab investigations revealed a CRP level of 13.5 mg/L and CSF analysis showing a WBC count of 59 cells/mm³ (polymorphonuclear cells of 23% and lymphocytes of 71%), RBC count of 3 cells/mm³, protein level of 0.43 g/L and glucose level of 54 mg/dL (serum glucose was 100 mg/dL). His blood and CSF cultures were negative for *Brucella* spp. and so were the AFB stain, culture, and MTB-PCR. Nevertheless, his *Brucella* serum serology revealed an antibody titer of 1:1280 for both, *B. melitensis* and *B. abortus*. He was admitted as a case of neurobrucellosis and was started on ceftriaxone 2 g IV every 12 h, amikacin 720 mg (7.5 mg/kg) IV every 12 h, doxycycline 100 mg orally every 12 h and rifampin 900 mg orally once daily. Ten days later, he started having spikes of fever reaching 40 °C, a thorough physical examination and work up were done and they were negative for any potential infection or reason for fever. Thus, antibiotic-induced fever was suspected due to ceftriaxone, thus, it was discontinued despite the overall improvement of the patient's central nervous system symptoms. Ceftriaxone was replaced with ciprofloxacin 400 mg IV every 8 h. As the fever persisted and liver enzymes were noted to increase, rifampin was stopped as well. In less than a week, rifampin was reintroduced. However, 90 min after the dose, the patient experienced shortness of breath, rash, swelling and redness of skin. His reaction was managed immediately with antihistamine and hydrocortisone. This allergic reaction was presumed to be attributed to rifampin; hence, it was stopped and never introduced again. Moreover, the patient also complained of reduced hearing in his right ear which was suspected to be due to an ototoxic effect of amikacin which resulted in its discontinuation. In order to enhance the management of neurobrucellosis, trimethoprim/sulfamethoxazole (TMP/SMX) double strength was started orally; yet, the patient had an episode of vomiting, so it was switched to IV which was well tolerated. Later on, as the patient was being prepared for discharge, IV TMP/SMX was stepped down to the oral formulation again. A lumbar puncture was repeated before discharge and showed an improvement from baseline with WBC count of 4 cells/mm³ (lymphocytes of 86%), RBC count of 9 cells/mm³, 0.33 g/L of protein and 61.2 mg/dL of glucose (serum glucose was not available at this point of time). Repeated antibody titers for *B. melitensis* and *B. abortus* were 1:640 and 1:320, respectively. The patient was discharged on doxycycline 100 mg orally every 12 h, ciprofloxacin 750 mg orally every 12 h and TMP/SMX double strength orally every 12 h. In his first outpatient visit one month

after discharge, the patient admitted to voluntarily discontinuing TMP/SMX due to severe episodes of vomiting and refused to take it again; however, he continued taking doxycycline and ciprofloxacin which resulted in clinical success (after a total of 18 weeks on doxycycline and 16 weeks on ciprofloxacin).

Case 4

A 25-years-old man who was previously healthy came to the hospital complaining of left lower limb pain that progressed to limb weakness with decreased ability to walk. Physical examination revealed moderate lower limb weakness with foot drop. It was worse on the left side with lower motor neuron lesion findings. He had normal sensory exam. He reported drinking raw camel milk three months before the first episode of pain with a family member who was diagnosed with brucellosis recently. There was no tuberculosis contact. Since the patient was suspected to have neurobrucellosis, lumbar puncture was done. CSF analysis showed a WBC count of 420 (polymorphonuclear cells of 4% and lymphocytes of 90%) cells/mm³, RBC count of 18 cells/mm³, elevated protein level at 2.45 g/L and glucose level of 21.6 mg/dL (serum glucose was 81 mg/dL). The CSF culture was positive for *Brucella* species. The acid fast bacilli stain and culture were negative, as well as the MTB-PCR. Other investigations including tests for hepatitis B and C viruses and human immunodeficiency virus (HIV) 1 and 2 were all negative. Serologically, antibody titers results from the CSF for *B. melitensis* and *B. abortus* were 1:160 and 1:80, respectively. His serum titers were not obtained initially. His CRP level was within normal limits. The patient refused to have a tuberculin skin test. An MRI of lumbosacral spine revealed enhancement of cauda equina nerve roots and surface of thecal sac, as well as L5-S1 degenerative changes with central posterior disc bulge indenting the ventral aspect of the thecal sac with no significant neural compromise associated with intervertebral disc dehydration (Image 3). He was admitted as a case of cauda equina syndrome secondary to neurobrucellosis and was started on ceftriaxone 2 g IV every 12 h, amikacin 500 mg IV every 8 h, doxycycline 100 mg orally every 12 h and rifampin 900 mg orally once daily. The initial plan was to continue the antibiotics with daily physiotherapy then re-evaluate after 6 weeks. However, two weeks into the treatment, the patient's status deteriorated significantly, from difficulty walking to being completely bed bound. Repeated work up showed no other significant findings. Furthermore, after 4 weeks of treatment, the patient started complaining of decreased hearing and pain in both ears resulted in discontinuation of amikacin. Six weeks into therapy, a repeated lumbar puncture did not show a significant improvement with a CSF analysis showing a WBC count of 315 cells/mm³ (polymorphonuclear cells of 41% and lymphocytes of 45%), RBC count of 15 cells/mm³, protein of 3.73 g/L and glucose level of 23.4 mg/dL (serum glucose was 82 mg/dL). Serum antibody titers were 1:320 and 1:80 for *B. melitensis* and *B. abortus*, respectively. Since the CSF repeated culture returned negative for *Brucella* spp., prednisone 1 mg/kg tapering dose was added aiming to reduce further nerve impingement. Luckily, the patient started to show clinical improvement and the IV ceftriaxone was discontinued after completing six weeks of treatment. The patient continued to restore his lower limb power and he was able to transfer to the wheelchair independently. Hence, he was discharged on doxycycline 100 mg orally every 12 h and rifampin 900 mg orally once daily for one year. The patient was scheduled for follow up in both the infectious diseases and neurology clinics. On his outpatient visits, the patient showed remarkable improvement of his lower limb weakness and he restored the ability to walk again using a cane. Serum antibody titers for both *Brucella* strains were at 1:80 and CRP remained within the normal range.

Case 5

A 60-year-old woman with a history of severe osteoporosis and previously treated tuberculous lymphadenitis, presented to the emergency department with fever she was experiencing daily for a month that did not respond to antipyretics. This was associated with frontal headache, night sweats, rigors, chills, generalized body ache, unintentional weight loss of 3–4 kg and pain in the lower back and right leg. She reported regular consumption of raw cheese. Investigational workup was done upon admission where a CSF analysis showed 8 cells/mm³ of WBCs (no differential was done), 12 cells/mm³ of RBCs, 0.36 g/L of protein and 54 mg/dL of glucose (serum glucose was not obtained). Blood CRP level was 36 mg/L. She was admitted as a case of possible bacterial meningitis with suspicion of neurobrucellosis. The patient was started on ceftriaxone 2 g IV daily. Three days later, her blood culture returned positive for *Brucella* spp., However the CSF culture was negative, as well as the AFB stain. Serological testing for hepatitis B and C viruses and HIV 1 and 2 were all negative. High antibody titers for both *B. melitensis* and *B. abortus* of 1:1280 were found in the serum whereas it was negative in the CSF. Ceftriaxone 2 g IV every 12 h was continued and prescribed for 6 weeks along with amikacin 400 mg IV every 12 h for the same duration, as well as doxycycline 100 mg orally every 12 h for 6 months and rifampin 900 mg orally once daily for 6 months. After about two weeks of treatment, lumbar puncture was repeated and the CSF showed no significant changes with WBC count of 7 cells/mm³, RBC count of 1 cells/mm³, protein of 0.33 g/L and glucose of 55.8 mg/dL (serum glucose was not available). During hospitalization, the patient felt generally better and became afebrile. After completing the IV antibiotics course (ceftriaxone and amikacin), lumbar puncture was ordered, but the patient refused to undergo the procedure. Consequently, the patient was discharged on doxycycline 100 mg orally every 12 h and rifampin 900 mg orally once daily for 6 months. During her follow up visits, the patient reported feeling well and afebrile with remarkable improvement of the headache. The follow up antibody titer was 1:320 for both *Brucella* strains, which continued to decrease until it reached 1:160 after completing 6 months of antibiotic therapy. As such, treatment was discontinued.

Case 6

A 44-year-old man with a history of recurrent epididymo-orchitis presented to the emergency department complaining of an on-and-off scrotal pain for the last 15 days and low grade fever for which he was given ciprofloxacin for 10 days and acetaminophen (paracetamol) from another hospital. This regimen helped managing his symptoms; however, they were not resolved rendering him seeking medical help at our institution. There were no histories of contact with a tuberculosis patient or raw milk consumption. On physical examination, his scrotum was enlarged, swollen and tender. An ultrasound revealed both testes were of normal size; however, there was bilateral significant increased vascularity in both testicles and both epididymal heads. The scrotal skin was not thickened. There was a slightly increased echogenicity of both testes and a small left hydrocele was identified.

There were a few (about four) tiny echogenic foci noted within the left testicle likely representing small calcifications. Physical examination findings of regional lymph nodes and skin were not significant. While awaiting other investigations, the patient was started on ciprofloxacin 400 mg IV every 12 h as an empiric therapy. Blood culture came back negative for *Brucella* spp.; however, antibody titers were positive for *B. melitensis* and *B. abortus* at 1:1280 for both strains. CRP level was 6.8 mg/L. The patient was diagnosed with *Brucella* epididymo-orchitis, but refused to undergo lumbar puncture for further investigation.

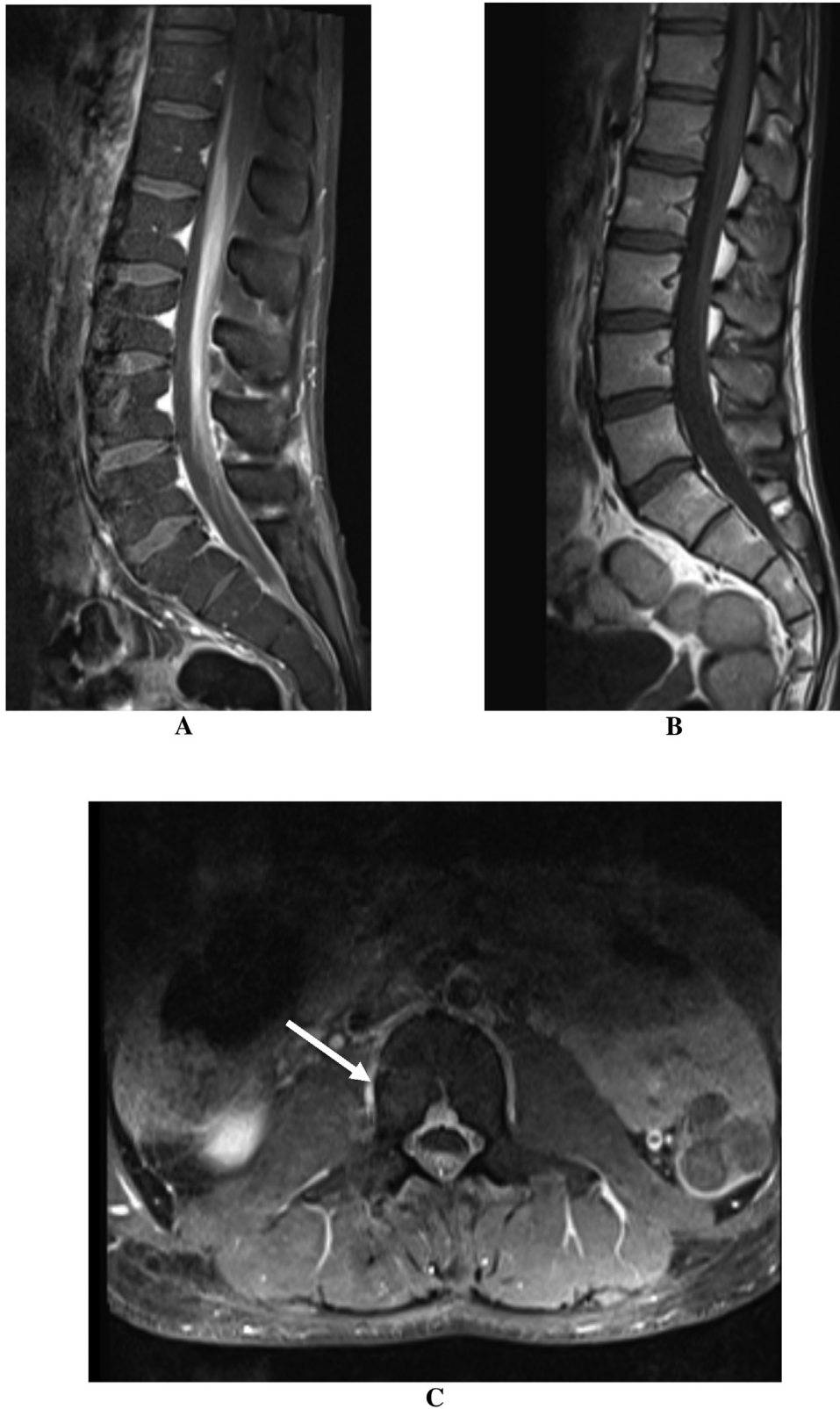


Image 3. Spinal magnetic resonance imaging of patient case 4 on T1 post contrast on sagittal and axial views showing enhancing cauda equina nerve roots.

Due to lack of clinical improvement, ciprofloxacin was discontinued three days later and was replaced by ceftriaxone 1 g IV every 12 h, doxycycline 100 mg orally every 12 h and rifampin 900 mg orally once daily. After two doses of 900 mg rifampin, the dose was decreased to 600 mg orally once daily though nothing in the

patient's notes indicated the reason for the dose change nor the liver enzymes were elevated. After ten days of treatment, ceftriaxone was stopped and the patient was discharged on doxycycline 100 mg orally every 12 h and rifampin 600 mg orally once daily for a minimum period of three months. Before

discharge, the patient was clinically improving as demonstrated by the decreased swelling and tenderness of his scrotum. On his first visit as an outpatient 2 weeks after discharge, the patient reported no new complications and appeared clinically well. Tests showed no signs of drug-induced hepatotoxicity, so the rifampin dose was increased to 900 mg orally once daily. On examination, his scrotum appeared to be relieved of the swelling and decreased in size. CRP level decreased slightly to 5.21 mg/L. A week later, the patient came again for follow up. While the patient did not show up for the next visit, his *Brucella* epididymoorchitis was deemed cured based on the improved clinical findings and decreased CRP. No repeated serology was done.

Discussion

As ceftriaxone has shown good *in vitro* activity against *B. melitensis*, its use in the clinical setting was seen in combination with other anti-*Brucella* antibiotics, especially for complicated brucellosis with good outcome [6,7]. In fact, a review by Pappas et al. on the management of neurobrucellosis recommended ceftriaxone as one of the first-line antibiotics given its efficacy that was reported in the literature [16]. In this article, ceftriaxone 2 g IV every 12 h was given to six patients who were diagnosed with brucellosis, confirmed either by culture, serology or both. Five patients were completely cured and one initially improved but was then lost to follow up. Table 1 shows patients' demographics and clinical outcomes.

Erdem et al. evaluated the outcomes of 215 neurobrucellosis patients retrospectively in a multicenter study [10]. Patients who received ceftriaxone-based regimens had significantly lower rates of failure and relapse compared with regimens that did not include the agent (6/166 [3.6%] versus 6/42 [14.3%]; $P=0.017$). Shorter

duration of therapy was also observed with regimens including ceftriaxone ($P=0.002$). Such findings correlate with the findings in the presented cases where ceftriaxone was associated with clinical success.

A recent case series by Zheng et al. studied three different treatment regimens in 17 neurobrucellosis patients [13]. Seven of the 17 patients received a regimen consisting of doxycycline, rifampin and ceftriaxone. Six patients had clinical cure though three suffered from complications and one was lost to follow up. The authors concluded that the addition of ceftriaxone in the initial therapy with doxycycline and rifampin resulted in better outcomes and higher cure rates than with the other combinations that included doxycycline plus rifampin with or without sulfamethoxazole. As the sample size was small, no statistical tests were conducted to confirm the significance of these findings.

Aygen et al. also assessed the impact of adding ceftriaxone to doxycycline and rifampin for initial therapy of neurobrucellosis in ten patients [9]. In this regimen, ceftriaxone was given in the first 2–3 weeks in combination with doxycycline and rifampin which were continued for a total duration of 8–24 weeks. No reported failure or relapses was observed in all ten cases. Thus, it was concluded that ceftriaxone and a third-generation cephalosporin with good CSF penetration profile, may be beneficial if given early in the treatment of neurobrucellosis with doxycycline and rifampin.

Similarly, eight of nine neurobrucellosis patients who received ceftriaxone as part of the treatment regimen had the infection eliminated, six were completely cured while two continued to have difficulty walking as reported in a case series by Gul et al. [11]. According to the report, the ninth patient was still in the intensive care unit.

An older report by Al-Idrissi et al. on 14 patients diagnosed with brucellosis and treated with ceftriaxone plus either rifampin or

Table 1
Summary of patients and outcomes.

Case No.	Patient Age (years)	Sex	Length of Stay (days)	Brucellosis Type	Antibiotics	Duration of Therapy (weeks)	Clinical Outcome
1	25	Male	21	Neurobrucellosis	Ceftriaxone Amikacin Doxycycline Rifampin	3 3 48 48	Cured with complications
2	54	Female	12	Uncomplicated brucellosis	Ceftriaxone Streptomycin Doxycycline Rifampin	6 6 12 12	Cured
3	31	Male	42	Neurobrucellosis	Ceftriaxone ^a Amikacin TMP/SMX Rifampin Doxycycline Ciprofloxacin	1 3 3 2 18 16	Cured
4	25	Male	48	Neurobrucellosis	Ceftriaxone Amikacin Doxycycline Rifampin	6 4 48 48	Cured
5	60	Female	42	Neurobrucellosis	Ceftriaxone Amikacin Doxycycline Rifampin	6 6 24 24	Cured
6	44	Male	10	<i>Brucella</i> epididymoorchitis	Ceftriaxone Ciprofloxacin Doxycycline Rifampin	1.5 0.5 12 12	Cured

TMP/SMX: trimethoprim/sulfamethoxazole.

^a Ceftriaxone was stopped after one week due to presumed antibiotic-induced fever.

streptomycin found immediate clinical response in nine patients (69.2%) [8]. Only one patient reported failure after the first dose. Although the therapy had to be changed in the remaining four patients (30.8%) to tetracycline plus streptomycin due to the lack of response after 5 days, it was concluded that ceftriaxone may be considered for brucellosis as a second-line therapy in patients when doxycycline is contraindicated.

A study by Koruk et al. on patients with *Brucella* endocarditis showed that none of the two patients who received a combination of ceftriaxone with an aminoglycoside died [12]. Moreover, mortality was only seen in three of 20 patients (15%) who received ceftriaxone with oral antibiotics compared with three patients of 12 (25%) who received a combination of oral antibiotics only. While a statistical analysis could not be performed given the small sample size, the study illustrates that adding ceftriaxone may have shown a mortality benefit.

Another study by Lang et al. on 18 acute brucellosis patients who were divided into two groups, ceftriaxone monotherapy group (n=8) versus doxycycline plus streptomycin group (n=10) [17]. Patients who received a monotherapy with IM ceftriaxone failed the therapy compared with the patients in the combination group who responded immediately to therapy. Six of the eight patients in the ceftriaxone group did not respond initially. However, after replacing ceftriaxone with a combination of doxycycline and streptomycin, immediate response was noted. One patient responded initially to therapy but experienced relapse within 3 weeks yet recovered when the doxycycline plus streptomycin regimen was started. Only one patient responded well and remained healthy at the end of the six months follow up period. Although authors of this report were reserved regarding recommending ceftriaxone for brucellosis treatment, it should be noted that ceftriaxone in this study was used alone rather than in combination as in the previously discussed reports that showed promising results.

In conclusion, based on data from this report and previous reports, we conclude that ceftriaxone administered at 2 g IV every 12 h in combination with doxycycline and rifampin represents a reasonable option as an initial treatment for complicated brucellosis, especially neurobrucellosis.

Author's contribution

Daniah F. Fatani: Data collection, Data interpretation, Drafted manuscript, Reviewed and updated manuscript per comments from other authors.

Walaa A. Alsanoosi: Data collection, Data interpretation, Assisted in manuscript drafting, Reviewed and updated manuscript per comments from other authors.

Mazen A. Badawi: Revision of data interpretation, Provided revisions on manuscript drafts.

Abrar K. Thabit: Generated the paper concept, Supervised the data collection, Revision of data interpretation, Provided revisions

on manuscript drafts, Reviewed and approved final version of the manuscript.

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