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Brucella infection following total joint arthroplasty: A systematic review of the literature

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ABSTRACT

Introduction: The aim of this systematic review was to analyze the results of published treatment options in Brucella infection following total joint arthroplasty (TJA).
Methods: We performed a systematic review of the literature regarding outcomes of Brucella infection after TJA (hip and knee). We searched multiple databases for articles in the area published from 1950 to 2016.
Results: A total of 18 patients (12 male and 6 female; mean age 59 years) from 14 published studies were identified. The minimum follow-up time was 6 months (range, 6–120 months). Seven patients were treated with debridement or antibrucella treatment only. Eleven patients (61%) underwent removal of the prosthesis and were treated with one or two-stage exchange arthroplasty. The mean duration of antibiotic therapy was 5.8 months. There was no relapse of infection.
Conclusions: In the absence of loosening of the components of the prosthesis, an attempt to treat Brucella infection medically might be a reasonable choice. One or two-stage exchange arthroplasty could provide successful results without relapse of infection when combined with appropriate antibiotherapy.
Level of evidence: Level III, therapeutic study.

Introduction

Brucellosis is a common zoonosis worldwide but predominantly affects the Persian Gulf, South America, India, Central Asia, and Mediterranean countries.[1] Transmission can occur via breaks in the skin in direct contact, through the ingestion of unpasteurized dairy products or raw meat, or through ingestion of aerosolized bacteria.[2] Brucella infection following total joint arthroplasty (TJA) is extremely rare and not quickly diagnosed.[3] This bacteria tend to be slow growing, so the culture period should be made longer than usual.[4] In the majority of cases diagnosis is serological and the low positiveness (15–20%) of the culture increases the period of no diagnosis.[5]

The generic name of Brucella includes a group of small gram-negative cocci and cocci rods that are aerobic, not mobile, with no spores. Six different species are known: *B melitensis*, *B abortus*, *B suis*, *B canis*, *B ovis*, and *B neotomae*.[6] These species are capable of surviving within phagocytic cells, making antibiotic treatment difficult.[2] Correct management for Brucellar infection diagnosed through aspiration or over a well fixed TJA is still unclear.[7] Traditionally, routine treatment usually includes the surgical removal of all bioprosthetic components.[3] Debridement without removal of prosthesis is a controversial issue due to the potential risk of relapse of infection. However, a few cases of Brucella prosthetic infection successfully treated with antibrucella agent alone without surgical treatment had been reported.[4,8] Due to the insufficiency of standardized clinical and evidence-based guidelines, there is no appropriate therapeutic schedule. In addition, the risk of relapse following treatment for Brucella prosthetic joint infection is unknown. Although a few reviews of single institution experience exist on this subject, an absence of systematic literature reviews about the outcomes of Brucella infection following TJA provides the impetus for this systematic review.

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The current study was designed to evaluate the epidemiology and treatment outcomes of Brucella infection after TJA with a review of the literature and pooled analysis. We therefore asked: (1) What are the treatment options for Brucella infection following total joint arthroplasty? (2) What are the outcomes of Brucella infection according to treatment modality?

Methods

Literature review

We performed a systematic review of the available literature using multiple separate search strategies. Four computer databases (PubMed, Web of Science, Embase, and Cochrane Library) were searched with the search words “arthroplasty”, “Brucella”, and “infection” in different combinations. Two independent reviewers separately completed the search, and the results were duplicated two times by each reviewer. The initial search was performed on June 10, 2016 with an update in August 10, 2016, to ensure accuracy. No additional study was identified by repeating the search.

Study inclusion

The inclusion criteria included (1) articles published from January 1, 1950 to January 10, 2016, (2) English-written articles in human species, (3) electronic publications that reported cases of Brucella infection, (4) both retrospective and prospective series, (5) only cases of Brucella infection after TJA, and (6) Only those articles that evaluated the final outcomes including reinfection.

The exclusion criteria included (1) conference presentations, (2) abstracts only, (3) articles without postoperative follow-up period and outcomes, (4) evaluation of any other lesion than the hip and knee joint, (5) native joint infection before arthroplasty, and (6) non-English articles. Due to the limited evidence available on the topic, case reports and case series were included in our study. Limits for the number of patients in each study or the minimum duration of follow-up were not used. Brucella infection following osteotomy and internal fixation was excluded.[9]

Study selection

Searching the aforementioned databases yielded a total of 64 articles. A simplified flow-chart depicting this process is seen in Fig. 1. A first search of the PubMed database yielded 19 articles and a second search of the Web of Science database with use of the same search strategy yielded 11 articles. There were 36 articles that appeared in more than one of the four searches yielding a total of 28 unique articles. Abstracts and full texts of the retrieved articles were read by 2 authors independently, and all relevant articles were read in full. In addition, we screened the references of the obtained articles for any additional studies. Disagreements regarding inclusion were resolved by discussion. Stringent exclusion criteria were applied, leaving 14 articles appropriate finally. Owing to a lack of prospective studies, most of the larger cohorts giving an answer or at least an insight to clinical problems were selected for this review. The Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline[10] was followed. Studies of Brucella infection after TJA predominantly started after the cases of Jones et al in 1983[3], although there had been several prior reports of osteoarticular infection due to brucella.[11]

Data extraction

Data were extracted from the included studies by two reviewers and checked by another. Where possible, corresponding authors were contacted to obtain missing data. The following data were extracted: demographics including age, gender, underlying disease, history of previous infection, risk factor, time to symptom after TJA, preoperative erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), diagnosis of Brucella infection, management of infection, postoperative antibrucella therapy, outcomes following treatment including clinical resolution, reactivation of infection, and other complications.

Results

Our systematic literature review of PubMed, Web of Science, Embase, and Cochrane literature searches revealed a total of 18 patients from 14 selected articles which have been reported from 1983 to 2015. Although complete data were not available, data such as age, gender, underlying medical/surgical conditions, reactivation of infection and postoperative complications were collected. Age, gender, pathogen organism, and antibiotic treatment were clearly identified in all the reports.

Epidemiology

There were 12 male patients and 6 female patients. The mean age of the patients was 59 years. The minimum follow-up was 6 months (range, 6–120 months). Demographic information is detailed in Table 1. The median duration from prosthesis implantation to the onset of symptoms was 3.9 years. It was difficult to analyze blood levels of CRP and ESR at presentation due to reporting inconsistencies (Table 2). Preoperative arthrocentesis and joint fluid cultures were performed in 13 patients and yielded negative culture results for 5 patients (38%). Eight patients (62%) were diagnosed with Brucella infection by Preoperative joint aspirates. B. melitensis was found to be the most common pathogen organism, with a pooled percentage of 78% (14/18). B. abortus was the second most common pathogen organism (22%). Additional history taken from the patients after the culture results revealed that almost all patients (94%) had a history of contact with livestock, or ingestion of unpasteurized dairy products (Table 3). Patient's history was not clearly reported in one study.[5]

Treatment

Eleven patients (61%) underwent removal of the prosthesis for initial treatment and were treated with one or two-stage exchange arthroplasty (Table 4). Two-stage exchange arthroplasty was performed in 8 patients (44%) with variable time frame between removal of the prosthesis and reimplantation (median 3.1 months, range 1.5–6 months). No patient underwent resection arthroplasty. Surgical debridement, retention of implant, and antibrucella therapy were performed in one patient.[7] Six patients were treated with antibrucella treatment only. The mean duration of antibiotic therapy for all patients was 5.8 months. Antibiotic therapy duration ranged from 6 weeks to 26 months, and the antibiotic treatment involved combination therapy with multiple agents (most commonly doxycycline, rifampin, and streptomycin). It was difficult to analyze the dose of antibrucella drugs due to a wide variation.

Outcomes

Mean duration of follow up after the surgical procedure was 3 years (range, 0.5–10 years). There was no relapse of infection. In one patient, at the time of the latest follow-up at three years, radiographs showed a radiolucent line at the femoral interface. There was no death related to the brucella infection following TJA and

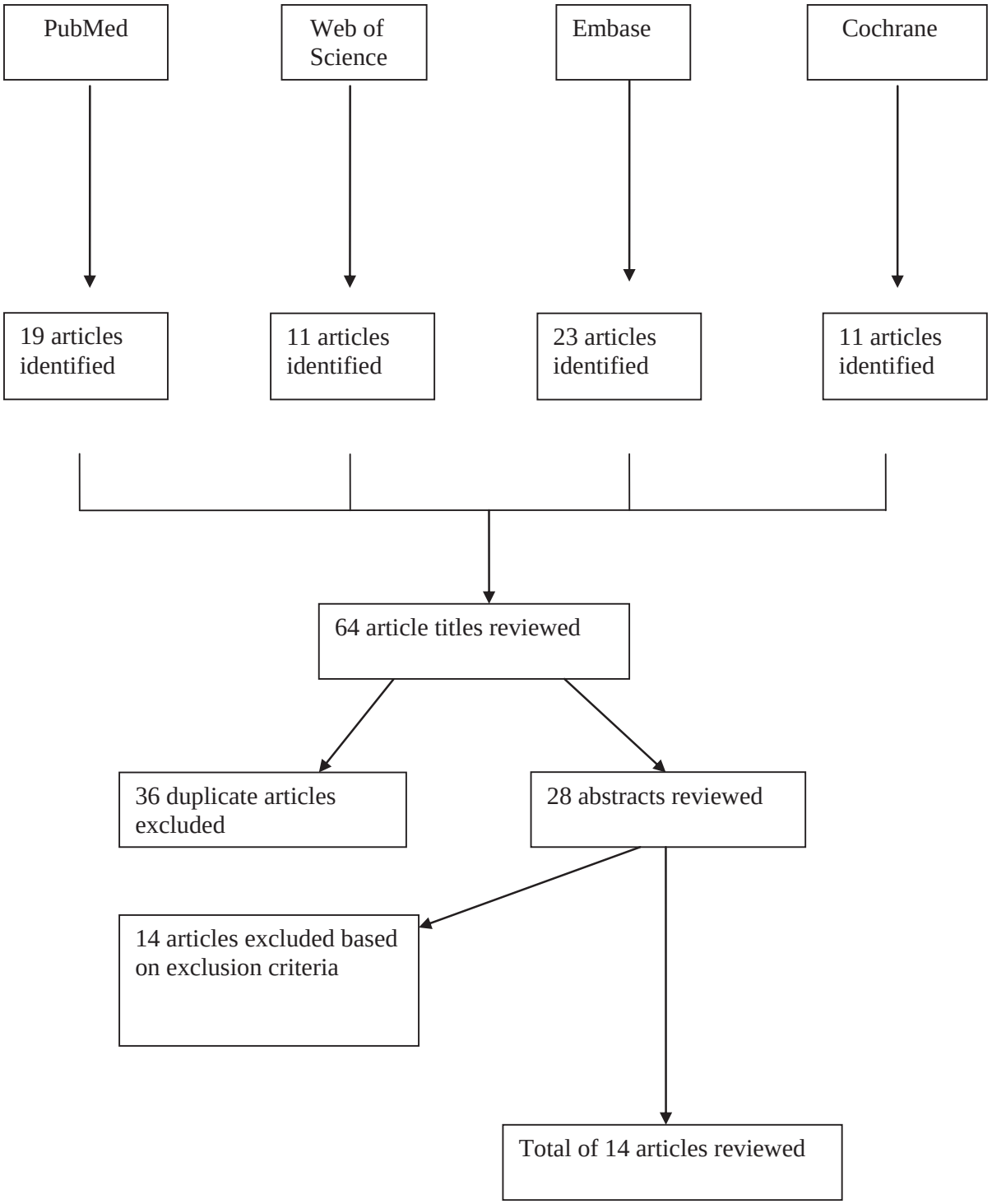

Fig. 1. The flowchart details the method of retrieval of relevant articles for this study.

deteriorating systemic brucellosis. No postoperative neurological or vascular complications were observed in any of the patients.

Discussion

Brucellosis is a zoonosis that generally causes systemic infection and affects osteoarticular tissue in 10%–85% of patients.[12] To date, prosthetic joint infection has been discussed extensively in the literature whereby staphylococci, streptococci and Gram-negative bacilli have been reported to be the most common causative organisms.[8,13,14] However, the treatment and outcome of Brucella infection involving prosthetic joints is not well known. The aim of this report was to evaluate the epidemiology and to give treatment recommendations of Brucella infection after TJA with a pooled analysis of the reported cases.

There are generally three ways for the infection to spread: by contaminated food or drinks, inhalation, or through small wounds in the skin.[15] Of these, however, the first one is surely the most

Table 1
Demographic information in the studies.

Author	Journal	Year	Country	Gender	Age	Location	UD or risk factor
Carothers	Am J Orthop	2015	USA	F	67	Hip	NA
Erdogan	Knee Surg Sports Traumatol Arthrosc	2010	Turkey	F	63	Knee	DM, previous infection
Dauty	Joint Bone Spine	2009	France	F	65	Knee	NA
Tassinari	Chir Organi Mov	2008	Italy	M	68	Knee	NA
Tena	Diagnostic Microbiology and Infectious Disease	2007	Spain	M	51	Hip	NA
Ruiz-Iban	Journal of Orthopaedic Surgery	2006	Spain	F	66	Hip	None
				M	71	Hip	None
Cairo	J Bone Joint Surg Am	2006	Spain	M	50	Hip	ON
				M	71	Hip	OA
Kasim	Scand J Infect Dis	2004	Lebanon	F	47	Hip	OA
Weil	Clinical Infectious Diseases	2003	Israel	M	38	Hip	Psoriatic arthritis
				M	64	Knee	Hip fusion
				M	67	Knee	OA
Ortega-Andreu	The Journal of Arthroplasty	2002	Spain	M	63	Hip	OA, heavy smoker
Orti	Eur. J. Clin. Microbiol. Infect. Dis	1997	Spain	M	60	Knee	hyperglycemia, nephrolithiasis, ON
malizos	Am J Orthop	1997	Greece	M	74	Knee	NA
Agarwal	Clin Orthop Relat Res	1991	Saudi Arabia	F	24	Knee	RA
Jones	Orthopedics	1983	USA	M	54	Hip	ON, OA

UD, underlying disease; NA, not available; DM, diabetes mellitus; ON, osteonecrosis; OA, osteoarthritis; RA, rheumatoid arthritis.

Table 2
Data on the studies.

Author	Symptom	Time to symptom after arthroplasty (years)	Admission radiographic finding	ESR/CRP	Aspiration	Joint fluid culture
Carothers	Thigh pain	2	Bone loss around cement	54/0.24	Yes (yellow synovial fluid)	Negative
Erdogan	Knee pain, chills, fever	2	No sign of implant loosening	43/18	Yes	Positive
Dauty	Discharge, fever	NA	Loosening of tibial plateau	60/80	Yes	Negative
Tassinari	Knee pain	2	Small area of resorption on tibial component	81/4.61	Yes (turbid yellowish corpuscolated fluid)	Positive
Tena	Hip pain, fever	5	Implant loosening	ESR 40	Yes (purulent fluid)	Positive
Ruiz-Iban	Thigh pain, groin pain	3	Radiolucent lines	increased	Yes	Positive
	Painless suppuration	2	Well-integrated	NA	No	No
Cairo	Intraoperative culture	Intraoperative culture	No loosening	ESR 123	No	No
	Hip pain, limping	3	Loosening	NA	No	No
Kasim	Hip pain	14	Loosening	ESR 88	No	No
Weil	Hip pain, fever	4	Loosening of femoral component	ESR 20	Yes	Negative
	Swollen, painful, warm knee	3	Loosening of both femoral and tibial components	NA	Yes	Negative (Acinetobacter baumanii)
	Fever, pelvic pain	14	Loosening of the femoral component.	ESR 76	Yes	Positive
Ortega-Andreu	Hip pain	5	Loosening of femoral component	NA	No	No
Orti	Knee pain	1	No loosening	57/64	Yes (serosanguineous synovial material)	Positive
Malizos	Synovitis, knee pain	0.3	No loosening	NA	Yes (serosanguineous synovial material)	Positive
Agarwal	Superficial infection, abscess	0.2	No loosening	NA	Yes (serosanguineous synovial material)	Positive
Jones	Fever	3	No loosening	ESR 36	Yes	Negative

NA, not available; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

common way.[5,16] Dairy products, especially soft cheeses, unpasteurized milk, and ice cream, are the most frequently implicated sources.[9] It is thought that the implant is infected by hematogenous spread of the microorganism at the time of systemic infection. Since the disease is still present, in varying trends, both in European countries and in the USA[17], screening for brucellosis is recommended for countries where brucellosis is still endemic[5] and the possibility of exposure exists (e.g., travel to or previous residence in endemic areas)[2].

Several reports comment on the ability to treat periprosthetic joint infection in the setting of well-fixed components with antibiotic therapy alone.[2,15] There is no general consensus regarding the type and dose of antibrucella agents that can be administered systemically to treat this challenging condition. Most authors suggested a minimum duration of antibrucella therapy of 6 weeks.[7,8,18,19] There is no evidence that a shorter period of antibrucella treatment will give the same results. In our pooled analysis, the mean duration of antifungal therapy was 5.8 months (range 6 weeks–26 months). Rifampin, doxycycline, and streptomycin have been considered the drugs of choice for administration in most report.[2,4,16,20] Selecting the appropriate antibrucella treatment requires a multiteam approach involving the treating orthopaedic surgeon, infectious disease specialists, and clinical pharmacologists. If removal of the arthroplasty is not an option (for

Table 3
History taken from the patient.

Author	History taken from the patient
Carothers	Febrile illness consistent with brucellosis
Erdogan	Nonpasteurized milk products, previous Brucella infection
Dauty	Unpasteurized goat cheese
Tassinari	Systemic infection from Brucella
Tena	Farmer with sheep, no history of raw milk ingestion
Ruiz-Iban	Contact with cattle
	Worked in an agricultural field
Cairo	Working with cattle
	Farmer contact with cattle
Kasim	Eating home-made cheese, prepared from unpasteurized fresh milk,
Weil	Ingestion of unpasteurized milk or goat cheese
	Ingestion of unpasteurized milk or goat cheese
	Ingestion of unpasteurized milk or goat cheese
Ortega-Andreu	Cattle owner
Orti	Worked with goats
Malizos	Shepherd
Agarwal	NA
Jones	Dairy farmer exposed to the infected cattle

NA, not available.

Table 4
Treatments and outcomes of the studies.

Author	Agglutination titer	Operation	Pathogen	Antibiotic treatment	Duration (months)	Follow up (years)	Outcome
Carothers	NA	Yes (2 stage)	B. abortus	Rifampin 600 mg, doxycycline 200 mg	5	2	No reinfection
Erdogan	640	No	B. melitensis	Rifampin 600 mg, doxycycline 200 mg	4	3	No reinfection
Dauty	NA	Yes (2 stage)	B. melitensis	Rifampin 900 mg, vibramycin 200 mg	1.5	10	No reinfection
Tassinari	800	No	B. melitensis	Rifampin 250 mg, doxycycline 200 mg	2	1	No reinfection
Tena	80	Yes (2 stage)	B. melitensis	Rifampin 900 mg, doxycycline 200 mg	2	4	No reinfection
Ruiz-Iban	NA	Yes (2 stage)	B. abortus	Rifampin 900 mg, doxycycline 200 mg	1.5	5.5	No reinfection
	640	Yes (drainage)	B. melitensis	Rifampin 900 mg, SM 1 g, doxycycline 200 mg	6	5	No reinfection
Cairo	320	No	B. melitensis	Doxycycline 200 mg, SM 1 g	26	5	No reinfection
	NA	Yes (1 stage)	B. melitensis	Rifampin 600 mg doxycycline 200 mg, SM 750 mg	6	3	No reinfection, radiolucent line at the femoral interface
Kasim	80	Yes (1 stage)	B. abortus	Vibramycin 200 mg, rifampin 600 mg	5	4	No reinfection,
Weil	1600	Yes (2 stage)	B. melitensis	Rifampin 600 mg doxycycline 200 mg	1.5	1	No reinfection
	1600	Yes (2 stage)	B. melitensis	Rifampin 600 mg doxycycline 200 mg	1.5	1	No reinfection
	1600	Yes (2 stage)	B. melitensis	Rifampin 600 mg doxycycline 200 mg	1.5	1	No reinfection
Ortega-Andreu	NA	Yes (2 stage)	B. melitensis	Rifampin 900 mg, SM 1 g, doxycycline 200 mg	3	0.5	No reinfection
Orti	160	No	B. melitensis	Rifampin 900 mg, SM 1 g, doxycycline 200 mg	1.5	0.7	No reinfection
Malizos	160	No	B. melitensis	SM 1 g, doxycycline 200 mg, Septrin Forte twice	7	2.6	No reinfection
Agarwal	2560	No	B. melitensis	Rifampin 300 mg, two septra tablets	19	1.6	No reinfection
Jones	640	Yes (1 stage)	B. abortus	Tetracycline 2 g, SM 1 g	12	3	No reinfection

NA, not available; SM, streptomycin.

instance due to the wishes of the patient or poor general condition), chronic suppression with antibrucella treatment could be recommended in the absence of loosening of the components of the prosthesis.[5] Further multicenter studies are needed to establish objective treatment guidelines for Brucella infection following TJA before this method attains widespread use.

According to a recent study, in cases of Brucella infection and loose components, surgical treatment (one- or two-stage revision) with appropriate antibiotic therapy was recommended.[2] In the present study, more than half of the patients (61%) underwent removal of the prosthesis for initial treatment and were treated with one or two-stage exchange arthroplasty. There was no relapse of infection after surgery. The ideal interval between implant removal and reimplantation is unknown. We found a mean of 3.1 months, with a range from 1.6 to 6 months. We recommend that that reimplantation should be performed only in the absence of clinical signs of infectious symptoms, with CRP and ESR serum levels within the normal range.[21] Additional 4–6 weeks of

combined antibiotic therapy after reimplantation is also recommended.[18,19] To the best of our knowledge, there exist currently no guidelines according to which Brucella periprosthetic infections should be locally managed. Nevertheless, we believe that impregnating the bone cement with antibiotics could be recommended, because Brucella joint infections have a high risk of subsequent other bacterial infections.[19] Even though antibiotic-loaded bone cement may not prevent relapse of Brucella infection, it could reduce the risk of other bacterial infection.[22] The incorporation of antibrucella drugs (streptomycin) into the methylmethacrylate powder used in cementing the replacement prosthesis has been reported previously.[3]

Of note, in cases of Brucella infection, the appropriate preventative measures to avoid transmission are necessary. Because of the nature of the surgical procedure (irrigation and debridement using pulse lavage), surgeons should be worried about aerosolization of Brucella bacteria and possible transmission to all staff present during the procedure.[2]

Limitations of this systematic review

Our study has some limitations. First, our study is limited by the quality of the studies we included. Due to the limited available evidence on antibrucella treatment for infection after TJA, we relied considerably on case reports and case series in this study. Second, because this is a pooled analysis of several retrospective case series with a heterogeneous cohort of patients, not all the data that we sought to include in our analysis was presented in sufficient detail to allow meaningful statistical inferences and comparisons.

Conclusion

In conclusion, in the consideration of Brucella periprosthetic joint infections treatment, one or two-stage exchange arthroplasty combined with adequate systemic antibiotic therapy is highly recommended. Local antibacterial drugs could be added to the cement especially when there is suspicious co-infection with other bacteria. In the setting of well-fixed components, Brucella infections can be managed conservatively with the combination antibiotic therapy. Additional prospective studies with involvement of larger number of patients with Brucella infection to include a wide range of ethnic backgrounds will help improve our ability to avoid the devastating outcomes.

Conflicts of interest

No conflicts declared.

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