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Brucellosis of Testis and Epididymis: A Review of the Literature

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Background: Brucellosis is a zoonotic disease which can afflict a number of organs and tissues. Brucellosis epididymo-orchitis (BEO), a complication of human brucellosis, can lead to other complications. In brucellosis non-endemic areas, some clinicians may be unfamiliar regarding the disease entity which may lead to delay in the diagnosis.
Aims: To review the literature on BEO, in order to document its presentation, diagnosis, management and outcome following treatment.
Methods: Various internet data bases were used to obtain literature on BEO.
Results/Literature Review: BEO (epididymitis plus or minus orchitis) is a complication of brucella species which can be transmitted by direct contact through the respiratory tract, skin, or conjunctiva, and through the gastrointestinal tract after ingestion of unpasteurized milk/milk products or raw infected meat. BEO may in endemic areas affect 2 to 20% of patients with brucellosis but the disease can also be encountered sporadically globally in non-endemic areas. BEO may at times be bilateral. The presentation of BEO is non-specific and it may be mistaken for non-specific epididymo-orchitis or epididymitis or testicular tumour or abscess. Ultrasound and MRI scan findings are not specific to BEO. Diagnosis of BEO may be established by (a) history of

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contact, (b) cultures from blood/epididymal aspirations, (c) various types of laboratory studies including (I) Culture, (II) Polymerase chain reaction (PCR), and (III) serology. Laboratory criteria for the diagnosis of Brucellosis is divided into (I) those for presumptive diagnosis and (II) those for confirmatory diagnosis: BEO can be effectively treated by means of combination chemotherapy for about six weeks but at times ochidectomy or drainage of testicular collection may be required for persistence of symptoms or suspicion of a tumour/testicular abscess. Relapses can occur therefore careful follow-up is required.

Conclusions: BEO can occur anywhere globally. A high index of suspicion is required from clinicians in order to establish early diagnosis. Most cases of BEO can be effectively treated with combination chemotherapy for about 6 weeks and triple antibiotic therapy would appear to be most effective and associated with absence or reduction of relapse.

Keywords: Brucellosis; epididymo-orchitis; orchitis; epididimytis; orchidectomy; antibiotics; rose Bengal test; PCR; culture.

1. INTRODUCTION

Brucellosis affecting human beings is a widespread Zoonosis which is mainly transmitted to humans from cattle, sheep, goats, pigs, and carriers by means of direct contact with blood, placenta fetuses, or uterine secretions or it may also be transmitted by means of consumption of raw animal products (especially unpasteurized milk and soft cheese) [1]. Globally, brucella melitensis is the most prevalent species responsible for causing human brucellosis, owing partly as a result of difficulties in immunizing free ranging goats and sheep [1]. In countries where eradication of brucellosis in animals (by means of vaccination and/or elimination of brucella infected animals) is not feasible, prevention of human infection is primarily based upon raising awareness of brucellosis, food safety measures, occupational hygiene, as well as laboratory safety [1]. In many countries brucellosis is a notifiable disease.

Brucellosis is not common in many countries and for this reason many clinicians would be unfamiliar with the presentation, investigation and management of this this disease. Because of global travel and importation of food from one country to another, rare cases including human brucellosis may be encountered sporadically in non-endemic areas. In view of this clinicians globally would need to be aware of human brucellosis and brucellosis epididymo-orchitis. The ensuing literature review on brucellosis of the testis and epididymis is divided into two parts (A) Overview and (B) miscellaneous narrations from some reported cases / case series.

2. METHODS

Various internet data bases were searched relating to case reports, case series, and miscellaneous documentations on brucellosis of the epididymis and brucellosis of the testis. Some of the data bases searched included: Google, Google scholar, PubMed, and Educus. The search words that were used included: Brucellosis; Brucellosis epididymo-orchitis; Brucellosis orchitis; Brucellosis epididimytis; Brucellosis of testis. In all 41 references were identified which were used for the literature review.

3. LITERATURE REVIEW

3.1 Overview: General Definition

Brucellosis is caused by (I) Brucella abortus, (II) or Brucella melitensis, (III) or Brucella suis [2] Brucellosis is named after Sir David Bruce who, in 1886, studied undulant fever or Malta fever [3] [4].

The causative factors of brucellosis are small aerobic Gram-negative rods of the genus Brucella, which currently is said to contain ten species namely: B. abortus, B. suis, B. ovis, B. melitensis, B. canis, B. neotomae, B. pinnipedialis, B. ceti, B. microti and B. inopinata. [5].

3.1.1 Alternative Terminology

Brucellosis is also referred to as (a) Malta fever and (b) undulant fever [6].

3.1.2 Epidemiology

Brucellosis affecting human beings is a zoonosis infection which may be acquired from any of the following: (1) sheep, (II) camels, (III) cattle, (IV) dogs, (V) goats, (VI) reindeer, or (VII) swine (through the skin / mucous membrane contact or

contaminated animal products) [1]. Brucellosis occurs on all inhabited continents and its course may be acute, sub-acute or chronic [5].

In brucellosis endemic areas the diagnosis may be easy for practitioners but in areas like United Kingdom and United States of America or other areas of the world it may be difficult to obtain history of consumption of cheese or milk from brucellosis endemic areas especially if these dairy products have been imported. Brucellosis is said to constitute a major health and economic problem in many parts of the world, encompassing the Mediterranean countries, and the Middle East [3,7,8]. Brucellosis is an important human disease in many parts of the world especially in the Mediterranean countries of Europe, North and East Africa, the Middle East, South and Central Asia, as well as Central and South America. There are only a few countries in the world which are officially free of the disease even though cases still occur in people returning from endemic areas [9]. Cases could also sporadically occur in residents in non-brucellosis endemic areas who consume cheese made out of unpasteurized milk. Brucellosis in humans tends to be occupational or food related (milk and cheese) [1]. Brucellosis of the testis and epididymis (brucellosis epididymoorchitis) occurs in 2% to 20% of cases of brucellosis [2,6,10].

3.1.3 Causative agent and mode of transmission

3.1.3.1 Causative agent

Causative agents of brucellosis in humans include: (I) *Brucella abortus*, biovars 1 – 6, 9; (II) *Brucella melitensis*, biovars 1- 3; *Brucella suis*, biovars 1, 3, and 4; *Brucella canis*, B; Suis, biovar 2 and B manis infections, have hardly been described [1]. It had been stated that in humans, brucellosis is mainly caused by: *B. melitensis* as the commonest pathogenic species, followed by *B. suis* and *B. abortus* is regarded as the mildest type of brucellosis [5]. Reservoirs and sources of human brucellosis include: (I) Cattle, (II) sheep, (III) goats, (IV) pigs, and scarcely, dogs and other animals and their products [1].

3.1.3.2 Modes of transmission

The modes of transmission of brucellosis include: (I) ingestion; (II) direct contact through breaks within the skin; (III) air-borne infection which can occur in laboratories and abattoirs. Human brucellosis primarily, afflicts (a) consumers of raw milk and raw milk derivatives, (b) farmers, (c) butchers, (d) veterinarians, and (e) laboratory workers [1].

It had also been stated that brucellosis infection in human beings occurs via penetration of damaged skin, conjunctiva, and more rarely via the alimentary route following consumption of infected products and that especially exposed are: Veterinarians, veterinary technicians, insemination service employees, zoo technicians, farmers, employees of slaughter houses and meat processing enterprises [5].

The incubation period of brucellosis is variable and ranges between 1 week and 2 months but usually the incubation period ranges between 2 weeks and 4 weeks [1].

3.1.4 Presentation

Generally, the presentation of brucellosis is non-specific which include (I) fever, (II) hepato-splenomegaly, (III) lymphadenopathy [2,11]. However, brucellosis involving the testis and or epididymis tends to present with (II) scrotal pain, (II) scrotal swelling, (III) and fever [2].

On the whole human brucellosis may manifest acutely or insidiously which may be in the form of (a) continued, intermittent, or irregular bouts of pyrexia of variable duration; (b) profuse sweating, (c) fatigue, (d) anorexia, (e) weight loss, (f) headache, (g) arthralgia, (h) and generalized aching [1].

Brucellosis of the testis and epididymis may present with testicular pain or swelling associated or not associated with non-specific symptoms but a history suggestive of a previous ingestion of un-processed milk or food from a brucellosis endemic area should alert the clinician to the possibility of brucellosis of the testis and epididymis [1].

The formation of an abscess is a rare complication associated with brucellosis [1]. In brucellosis most of the causes of death were due to brucella endocarditis and neuro-brucellosis [1].

3.1.5 Diagnosis

In general diagnosis of brucellosis may include: (a) culture of a brucella organism and (b) serologic tests which permit the detection of antibodies which occur in response to infection,

Some of methods used in the detection of the antibodies include: agglutination test, complement fixation test, Coombs test, 2-mercaptoethanol agglutination test ('reduction' reaction), and Burnet's intradermal allergy test (Burnet's skin allergy test) which detects the state of hypersensitivity of the infected organism to *Brucella abortus* rods [5].

Diagnosis of brucellosis epididymo-orchitis would requires a high index of suspicion

(I) History - A history of residence or previous residence in a brucellosis endemic area would be helpful in alerting the clinician to the possibility of brucellosis; a history of consumption of cheese, milk or the aforementioned meat products from an endemic area would also be helpful in alerting the clinician to the possibility of brucellosis

(II) Laboratory studies which are used to confirm diagnosis of brucellosis include: (a) Culture, (b) Polymerase chain reaction (PCR), and (c) serology [1].

Laboratory criteria for the diagnosis of brucellosis is divided into (I) those for presumptive diagnosis and (II) those for confirmatory diagnosis which are detailed as follows: [1].

3.1.5.1 Presumptive diagnosis

(a) Rose Bengal test (RBT) is used in the screening for brucellosis and positive tests would need to be confirmed by one of the tests listed below under confirmatory diagnosis.

(b) Standard agglutination test (SAT)

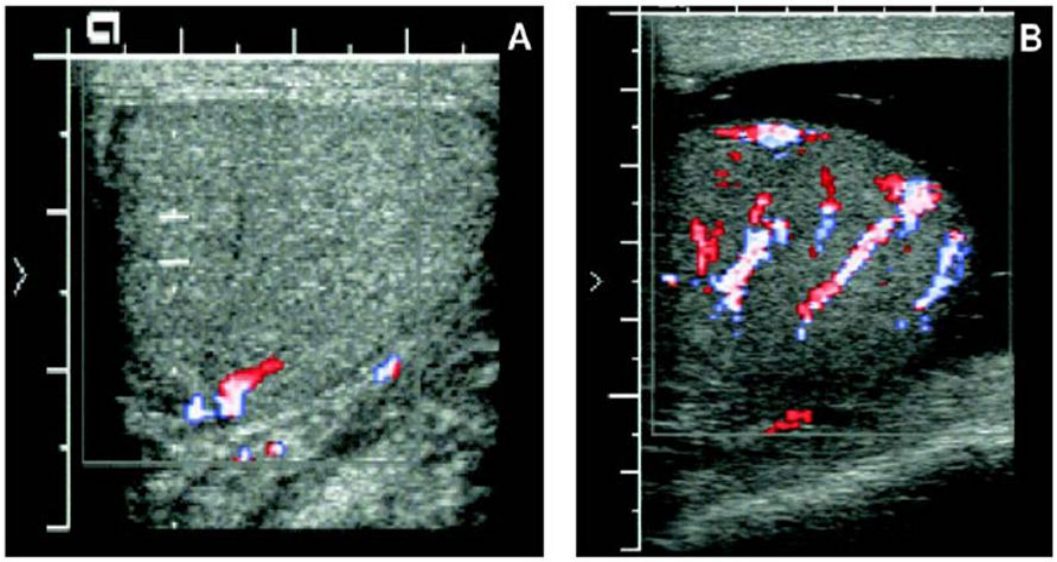

Fig. 1. Testicular ultrasound showing a normal blood flow to the right testicle (A) and increased blood flow to the left testicle (B)

This figure was reproduced from [36] Al-Tawfiq J A. Brucella epididymo-orchitis: a consideration in endemic area. International Braz. J. Urol. 2006 May-Jun; 32(3):
URL: http://dx.doi.org/10.1590/51677-5538]

3.1.5.2 Confirmatory diagnosis

(a) Isolation of Brucella spp. from blood or other clinical specimen
(b) Presumptive laboratory diagnosis which has been based upon the detection of agglutinating antibodies (RBT and SAT) in combination with the detection of non-agglutinating antibodies through:
(c) Elisa IgG test;
(d) Coombs IgG test

PCR and new rapid tests such as lateral flow tests have been developed.

3.1.6 Radiological features

3.1.6.1 Ultrasound scan

Ultrasound scan may reveal a hypo-echoic testicular mass [10] [12] but it should be noted that this is not diagnostic. Color Doppler ultrasound scan may sometimes reveal increased vascularity of the mass in the testis [7] [10] or epididymis which is not specific for brucellosis but this may make the clinician wonder whether or not the lesion is a malignancy. Nevertheless, scrotal ultrasound scan findings in brucellosis epididymo-orchitis are not specific (see Figs. 1, 2 and 3 for examples).

3.1.7 Magnetic resonance imaging (MRI) scan

Magnetic Resonance Imaging Scan can also be used to assess Brucellosis Epididymo-orchitis but the findings are not specifically diagnostic of brucellosis (See Fig. 4 for an example of MRI scan finding of a patient who had brucellosis epididymo-orchitis).

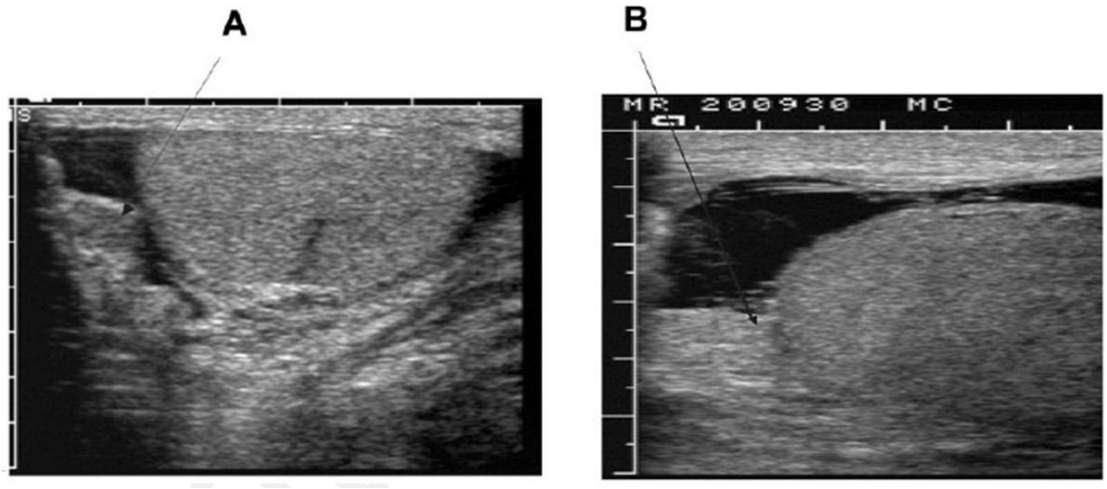

Fig. 2. Testicular ultrasound showing a normal right epididymis (A) and an enlarged and thickened left epididymis (B)

This figure was reproduced from [36] Al-Tawfiq J A. Brucella epididymo-orchitis: a consideration in endemic area. International Braz. J. Urol. 2006 May-Jun; 32(3):
URL: http://dx.doi.org/10.1590/51677-5538]

3.1.7.1 Macroscopic description

Gross examination of a testicular mass involved with brucellosis may not look any different from a testicular tumour with naked eye inspection as was found in [6] [10]. Macroscopic examination may reveal a solid, gray-white mass and at times evidence of complete destruction of the testis [12].

3.1.7.2 Microscopic features

In brucellosis orchitis, epididymitis or epididumoorchitis, microscopic examination of the testis and or epididymis tends to reveal features of granulomatous [2] or testicular abscess or it may reveal: [12]

(I) Follicular hyperplasia, clusters of epithelioid histiocytes which may form large non-caseating granulomas [2].
(II) Eosinophils, plasma cells and immunoblasts [2].

3.1.8 Differential Diagnosis

The differential diagnoses include non-specific epididymo-orchitis, other types of granulomatous epididymitis/epididymo-orchitis and various types of testicular tumours. as well as testicular abscess.

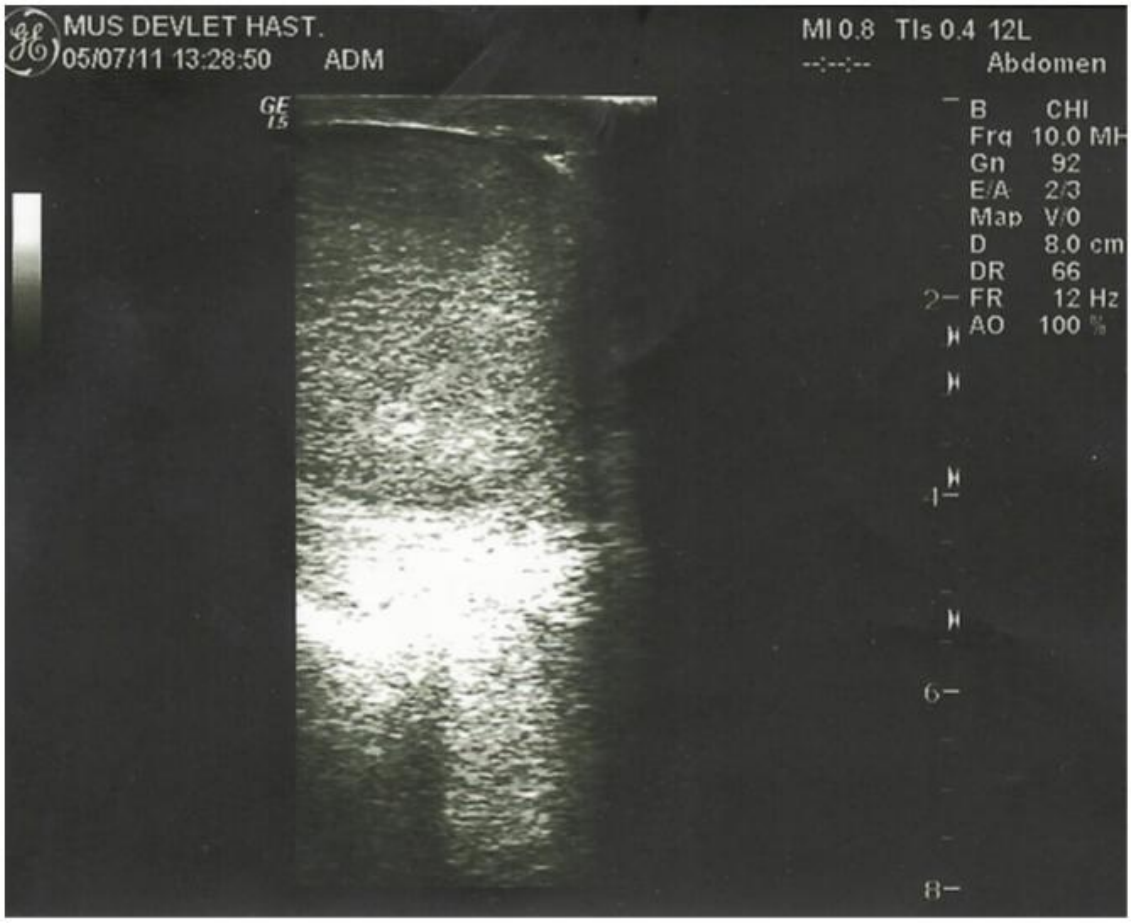

Fig. 3. Scrotal Doppler Ultrasound Image of a patient with Brucellosis epididymo0-orchitis

This figure shows an ultrasound scan of testis afflicted by Brucelloss epididiymo-orchitis reproduced from [7] Karakose A, Yuksel M B, Aydogdu O, Hamidi A A, Epididymoorchitis as the First Finding in Patients with Brucellosis. Advances in Urology Volume 2013 (2013), Article ID 765023, 4 pages http://dxdoi.org/10.1155/2013/765023 with permission granted under Creative Commons Attribution license ultrasound scan was not reported in the paper but the finding here is non-specific.

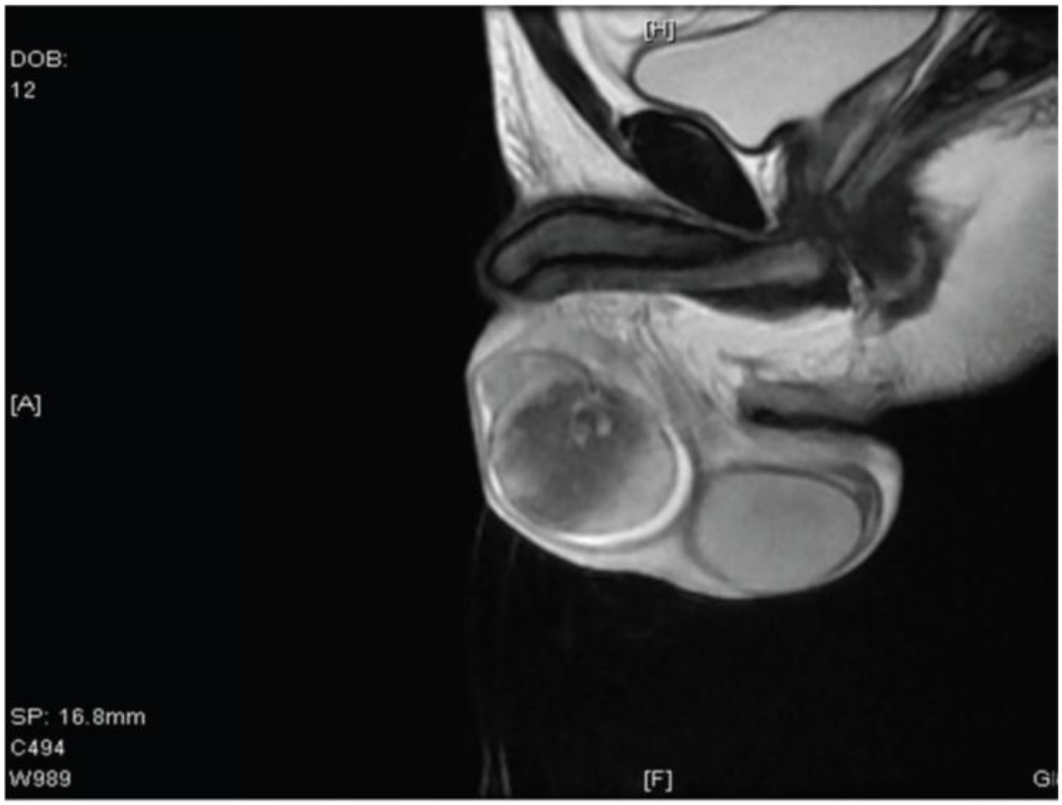

Fig. 4. Scrotal MRI image of a patient with Brucellosis Epididymo-orchitis

Taken from [7] Karakose A, Yuksel M B, Aydogdu O, Hamidi A A, Epididymoorchitis as the First Finding in Patients with Brucellosis. Advances in Urology Volume 2013 (2013), Article ID 765023, 4 pages http://dxdoi.org/10.1155/2013/765023 with permission granted under Creative Commons Attribution liche ultrasound scan was not reported in the paper This figure though unreported would appear to show an area of low signal in the right testis which would not be specific for brucellosis orchitis only.

3.1.9 Treatment

The key points on treatment of uncomplicated brucellosis in humans iterated by WHO include: The essential element in the treatment of all forms of human brucellosis is the administration of effective antibiotics for an adequate length of time, treatment of uncomplicated cases in adults and children eight years of age and older would require doxycycline 100 mg twice per day for six weeks plus streptomycin 1 gram daily for two to three weeks or doxycycline 100 mg twice per day for six weeks plus rifampicin 600 mg to 900 mg daily for six weeks [9].

Brucellosis orchitis, epididymitis or epididymoorchitis is treated with antibiotics; however, orchiectomy has been undertaken if the lesion resembled a neoplasm or it has been refractory to therapy [1].

The antibiotic treatment of brucellosis can be summarized as follows [1]:

(I) Doxycycline 100 mg twice a day for 45 days + streptomycin 1 gram daily for 15 days [1].

(II) The main alternative to the above treatment is Doxycycline 100 mg twice a day for 45 days + rifampicin 15 mg / kg / day (600 mg to 900 mg) for 45 days [1].

(III) It had been stated that experience would suggest that streptomycin may be substituted with gentamicin 5 mg / kg for 7 days to 10 days (Doxycycline 100 mg twice a day for 45 days plus gentamicin 5 mg / kg for 7 days to 10 days); however, there has been no study directly comparing both treatment regimens [1].

(IV) Optimal treatment for neonates and children under 8 years old has not yet been determined; nevertheless, for

children there has been some experience with trimethoprim/sulfamethoxazole (cotrimoxazole) in combination with an aminoglycoside (streptomycin, gentamicin) or rifampicin [1].

(V) A study was reported by Bayindir et al. [13] in which, 3-antibiotic treatment regimen containing streptomycin plus doxycycline and rifampicin (SDR) had been compared with 2-antibiotic treatment regimen (doxycycline and rifampicin also called DR) in complicated brucellar spondylitis. It was found that the 3-antibiotic treatment regimen was efficacious and associated with full recovery and without failure and relapse. Bayindir et al. [13] studied 1002 patients. They reported that twenty patients received streptomycin 1 gram per day intramuscularly for 15 days and tetracycline hydrochloride 500 mg orally every six hours for 45 days (ST group), 21 patients had daily intramuscular injections of streptomycin for 15 days and doxycycline 100 mg twice daily for 45 days (SD group), 20 patients received doxycycline 100 mg twice daily for 45 days and rifampicin 15 mg per kilogram per day in a single morning dose for 45 days (DR group), 19 patients had received ofloxacin, 200 mg every 12 hourly orally for 45 days and rifampicin 15 mg per kilogram per day in a single morning dose for 45 days (OR group), and 22 patients received streptomycin 1 gram per day intramuscularly for 15 days and doxycycline 100 mg orally twice per day for 45 days plus rifampicin 15 mg per kilogram in a single morning dose for 45 days (SDR group). With regard to the results, initial failure of therapy was reported in 2 patients (10%) in the ST treatment group, 4 patients in the SD group (19%) in the SD group, 3 patients (15%) in the DR group, and 5 patients (26%) in the OR treatment group. Furthermore, 2 patients (10%) within the DR treatment group and 5 patients (26%) in the OR treatment group experienced relapse during the follow-up period. No relapse was reported in patients that were in the ST, SD, and SDR treatment groups. The response rates were 90% in the ST treatment group and 81% in the SD treatment group. On the contrary, maximum good response (100%) and no relapse were observed in the SDR treatment group. As a result of the aforementioned findings, the authors concluded that they would recommend the use of a combination of streptomycin, doxycycline, and rifampicin (triple antibiotic treatment regimen) as therapy for brucellar spondylitis and to reduce relapse rates. The results of this study would suggest that the use of 3-antibiotic treatment regimen would be more effective in comparison with 2-antibiotic treatment regimens with regard to response to treatment and relapse. In another study comparing two durations of triple-drug therapy in uncomplicated brucellosis, Sofian et al. [14] compared a triple-drug regimen of doxycycline plus rifampicin for 6 weeks and streptomycin for the first 7 days with doxycycline plus rifampicin for 8 weeks and streptomycin for 7 days in patients with uncomplicated brucellosis. The primary outcome measure for the two treatment groups was the relapse rates which were measured at 1, 3, 6, 12, and 24 months following cessation of therapy. With regard to outcome, no significant difference was found in the relapse rate of the 8 week treatment group when compared with the 6-week treatment group (9.7% versus 13.9%). No significant differences were observed between the 6-week treatment group and the 8-week treatment group with regard to the relapse rate, the period between clinical presentation and commencement of treatment, and time of relapse. Resolution of symptoms occurred in all of the cases at a median period of 9.5 days and none of the cases experienced continuing symptoms after treatment. The authors concluded that their study did not find any differences between the two treatment groups. They recommended that further comparative studies with a large sample size should be carried out in order to achieve a consistent therapeutic regimen for uncomplicated brucellosis, to help identify those who may benefit from longer treatment and to minimize adverse effects and unnecessary continuation of treatment.

3.1.10 Outcome

It would appear that following a long period of combined antibiotic therapy for brucellosis with any of the aforementioned treatment options, the prognosis is good; however, following a shorter period of antibiotic therapy there is the likelihood

that relapses or chronic/persistent brucellosis epididymo-orchitis may develop.

3.1.11 Prevention

In order to reduce the incidence of brucellosis, there is need to adopt the following strategies:

- If there a diagnosis of brucellosis then full and complete treatment would be necessary [1].
- Global Education to avoid consumption of un-pasteurized milk and milk derivatives [1].
- Barrier precautions for hunters and professionals at risk including: butchers, farmers, slaughterers, veterinarians [1].
- Careful handling and disposal of after-births, especially in cases of abortion [1]

Serological or other testing of animals; Immunization of herds / flocks may be envisaged; elimination of infected herd / flocks [1].

3.2 Miscellaneous Narrations and Discussions from Some Reported Cases

See table 1 which shows a list of some of the reported cases of brucellosis of the testis and epididymis with treatment and outcome.

Table 1. List of some of the reported cases of brucellosis of the testis and epididymis with treatment and outcome

Authors / Reference /Age / Duration of symptoms at diagnosis	Side and diagnosis	Treatment	Outcome
Hizli and Uygur [10] 22 years; 3 months	Bilateral; Ig G positive test for Brucellosis	Right radical orchidectomy plus left testis sparing surgery; plus 1 gram of ciprofloxacin per day for six weeks plus 200 mg per day of doxycycline for 6 weeks	His IgG test for Brucellosis was negative at 3 months; seminal analysis revealed he had oligospermia; He had remained asymptomatic for 6 months.
Koçak et al. [12] 32 years; 2 months history of left testicular pain and a 3-year past history of systemic brucellosis without epididymoorchitis.	Left; positive STA test for brucellosis (1/80); but testicular tumour could not be excluded despite this	3 years earlier he was treated with rifampicin and doxycycline for systemic brucellosis with full recovery and return of serum standard agglutination test (STA) for brucellosis to normal Left radical orchidectomy with final diagnosis of brucellosis abscess on histology; ciprofloxacin 1 gram per day plus doxycycline 200 mg per day for 6 weeks	He recovered fully with his Brucellosis STA test result returning to normal after 2 months. No long term outcome available to author
Navarro-Martinez et al. [22] 59 cases of brucellosis epididymoorchitis 15 years to 79 years; [1991 – 1999]	Details of sites not available In 41 patients (69%), Brucella species was isolated from blood cultures and in 4 patients Brucella species was isolated	39 patients were treated doxycycline and aminoglycosides; 10 patients had doxycycline and rifampicin; 3 patients had trimethoprim-sulfamethoxazole with	In 9 patients (15%), the infection had failed to respond to treatment; 15 patients (25%) had experienced relapse of the disease; 3 patients who had

	from aspirates from the epididymis.	rifampicin; 7 patients had trimethoprim-sulfamethoxazole as monotherapy. The duration of treatment ranged between 21 days and 90 days with a median duration of 45 days.	necrotizing orchitis who did not respond to antibiotic treatment underwent orchidectomy; on the whole classical brucellosis therapy was adequate for the treatment of brucellosis epididymoorchitis.
Akinci et al. [35] reported on 17 cases [2001 to 2004]	11 patients had unilateral epididymoorchitis; 4 had unilateral orchitis; 1 had unilateral epididymitis; 1 had testicular abscess	Combined antibiotic therapy was given for 6 to 8 weeks (details not available to author); two patients underwent orchidectomy; out of 14 patients who had semen analysis, 5 patients had azospermia and 8 had oligospermia.	1 patient experienced relapse, 3 had permanent oligospermia, 1 patient had permanent azospermia following antibiotic therapy
Al-Tawfiq [36]. 41 year-old 2 weeks history of general symptoms and 2 days testicular pain	Left epididymoorchitis. His Brucella abortus antibody titre was < 1:160 for IgG, > 1:2560 for IgM	Doxycycline for 6 weeks plus gentamicin for 2 weeks.	Complete resolution of symptoms and signs.
Sevim et al. [6] 15 days of symptoms	Right epididymoorchitis. Rose Bengal test positive, Wright agglutination test 1:640 (positive).	Initially ciprofloxacin 500 mg twice daily and dexketoprofein 25 mg twice per but symptoms did not improve; Rifampicin 600 mg three times per day for 6 weeks, plus doxycycline 200 mg per day for 6 weeks, plus streptomycin 1 gr/g's for two weeks, plus non-steroidal anti-inflammatory therapy.	15 days after his treatment was started his symptoms and signs had completely disappeared but he was advised to complete a 6-week course of rifampicin 600 mg per day and doxycycline 200 mg per day and to return for follow-up.
Afsar et al. [27] reported on 13 patients who were diagnosed with brucellosis epididymo-orchitis between 1989 and 1991	In 8 patients both the testis and epididymis were involved, 3 had bilateral epididymoorchitis, 2 had epididymitis alone	Doxycycline 200 mg daily for 6 weeks and rifampicin 600 mg daily for 6 weeks.	10 patients had complete resolution
Yurdakul et al. [30] reported a study of 84 patients who had been diagnosed with epididymo-orchitis between July 1987 and September 1993.	14 patients out of 84 with epididymoorchitis had brucellosis epididymoorchitis) (17%). All 14 patients had elevated agglutination titers; Brucella blood culture was positive in 4 (28.5%) of the 14	Standard therapy regimen which consisted of streptomycin and tetracycline was used (details of duration not available to author).	Treatment which consisted of streptomycin and tetracycline was effective in 13 of 14 (93%) of cases

	patients;		
Khan et al. [18] reported a series of 40 patients who were diagnosed with epididymo-orchitis between January 1983 and August 1985.	In 14 of the cases, brucellosis was diagnosed, in 10 of the 14 cases both the testis and epididymis were in involved (epididymoorchitis), 1 patient had bilateral disease.	All the 14 patients were treated with streptomycin and tetracycline (duration not available to author)	8 patients (57%) experienced complete resolution
Gul et al. [40] reported on 19 patients who were diagnosed with epididymo-orchitis due to brucella melitensis between 1998 and 2005	Diagnosis of brucella epididymitis was made by isolating Brucella species from blood culture or epididymal aspirations or by standard tube agglutination testing and slide agglutination testing together with clinical findings. Seven cases (36.8%) had undulant fever. Brucella species was isolated from blood cultures in 11 patients and from epididymal aspirations in 3 patients. Rose Bengal tests were positive in all of the patients.	6-week treatment. (Details not available to author)	Total recovery was achieved in 12 patients with a 6-week treatment. Five patients (26.3%) did not respond to therapy and another 2 (10.5%) had relapsed.
Naiafi et al. [41] reported 30 cases of Brucella epididymitis in two hospitals between 1997 and 2009.	The average age was 22.5 ± 12.43 years.	Different treatment regimens were given including doxycycline plus rifampin in 60% of the cases, doxycycline plus rifampin plus aminoglycoside for the first two weeks (36.6%) and doxycycline plus cotrimoxazole were given in 3.4% of the patients.	Ten percent of the patients did not respond to antibiotic therapy and they required surgical drainage or orchiectomy.

Hizli and Uygur [10] reported a 22-year-old man who presented with a three month history of right testicular mass. His clinical examination revealed a solid painless mass in the right testis and a slightly enlarged palpable mass in the left testis. He had scrotal ultra-sound scan which revealed a hypo-echoic heterogeneous mass, in the right testis and a mass in the upper pole of the left testis. Color Doppler scanning of the mass had revealed central vascularization which resembled a testicular tumour. His serum Beta Human Chorionic Gonadotropin (ß-HCG) and alpha-fetoprotein (AFP) levels as well as white blood cell count were normal. He also had computed tomography (CT) scans of his abdomen and thorax which were normal. He underwent right radical orchidectomy and left testis sparing surgery. Histological examination of specimens of both testes revealed granulomatous orchitis with focal necrosis. Upon the pathologists realization that the patient had been a shepherd and that he had been living in a brucellosis endemic area, the pathologist recommended that the patient should be investigated for brucellosis.

His immunoglobin G (IgG) test was positive for brucellosis and his immunoglobin M (IgM) was negative. Pursuant to the final diagnosis of brucellosis of the testis, the patient was treated with 1 gram per day of ciprofloxacin plus 200mg per day of doxycycline for 6 weeks. Three months post-operatively the patient's follow-up brucellosis IgG and IgM levels were negative. He had semen analysis which revealed oligospermia with a sperm count of 3 million per ml and his serum testosterone level was normal. He had remained asymptomatic for six months following his operation. It would be argued that lessons learnt from this case would indicate that if the clinicians had been aware of the fact that the patient was a shepherd who lived in a brucellosis endemic area perhaps they would have pre-operatively performed laboratory tests to exclude brucellosis or they would have undertaken testicular biopsies for frozen section examination which would have indicated a diagnosis of brucellosis of the testis. Lessons learnt from this case would indicate that not all vascularized testicular masses indicate malignancy and that other rare testicular pathologies including brucellosis should be considered in cases of testicular lumps in patients living in brucellosis endemic areas and a thorough history of occupation and exposure to a source of brucellosis should be undertaken in order to avoid unnecessary extensive surgery. It would also be argued that perhaps in a case when a patient with a testicular mass living in a brucellosis-endemic area is being investigated the patient should have pre-operative biopsy of the testicular lump even though this is not recommended for testicular cancer.

Koçak et al. [12] reported a 32-year-old man who presented with a 2-month history of a painless left testicular mass. He had a 3-year past history of systemic brucellosis without epididymoorchitis. He had been treated with rifampicin plus doxycycline with complete recovery including normalization of his serum standard agglutination test (STA). His right testis was found to be normal on palpation; however, the left testis was found to be indurated and non-tender. He had ultra-sound scan of testes which revealed a hypo-echoic, completely heterogeneous mass within the left testis; Color Doppler scan revealed no evidence of hyperemia or increased blood flow. The ultrasound scan findings were adjudged to be compatible with non-seminomatous tumour. His serum Beta Human Chorionic Gonadotropin (ß-HCG) and alpha-fetoprotein (AFP) levels were normal and his leucocyte count was 15100/µL. His serum STA test for brucellosis was 1/80, which was positive. Based upon the results a diagnosis of an abscess forming brucellosis of the testis was made; however, testicular tumour could not be completely excluded. A left radical orchidectomy was performed and macroscopic examination of the specimen revealed a solid, gray-white mass, resulting in an almost complete destruction of the testis. Histological examination of the specimen revealed chronic granulomatous inflammation of the left testis which contained dense lymphoplasmacytic infiltration. Ziehl-Neelsen staining of the specimen for acid resistant bacilli was negative. A final diagnosis of brucellosis abscess of the left testis was made. He was treated with 1 gram per day of ciprofloxacin plus 200 mg of doxycycline for six weeks. He recovered clinically and his STA titers were found to be undetectable after 2 months. Koçak et al. [12] stated the following:

- With regard to acute brucellosis, positive blood cultures had been obtained in 10% to 30% of cases and the positivity decreases with increased duration of the illness; In view of this majority of cases of brucellosis are diagnosed by means of STA test.
- Salata [15] had indicated that in cases of chronic localized brucellosis, STA levels may be absent or low in that the STA titers tend to be less than 1/160 as a result of prozone phenomenon which would indicate presence of immunoglobulin A and G blocking antibodies.
- Brucellosis orchitis tends to be diagnosed by means of serological tests, by ultrasound scan, by the elucidation of symptoms including: pyrexia, testicular pain, testicular enlargement and redness.
- Even though orchitis is the commonest form of brucellosis in the genitourinary tract, prostatitis and abscesses of the testis may also be encountered as a complication of primary infection as reported by a number of authors [15-19].
- The treatment of brucellosis by means of a variety of medications for example, rifampicin, doxycycline, tetracycline, ciprofloxacin, cotrimoxazole and streptomycin, had been reported by some authors [15,16] to be effective in 90% of cases, and associated with a relapse rate of 10%.
- Relapse of brucellosis could manifest as long as 2 years pursuant to successful

treatment; nevertheless, relapse of brucellosis as orchitis had only been scarcely reported previously [19,20] with systemic symptoms.
- Their reported case was the first case of brucellosis relapse diagnosed with an isolated testicular abscess without any evidence of systemic symptoms.
- Despite developments and progress in therapeutic regimens for brucellosis, it had been reported that orchidectomy may be undertaken following the development of testicular abscesses and poor response to treatment in primary brucellosis [21].

Navarro-Martinez et al. [22] studied 59 cases of brucella epididymoorchitis (BEO) between 1991 and 1999. They reported that:

- The patients' ages ranged between 15 years and 75 years and their median age was 34 years.
- 46 patients (78%) presented with acute symptoms; All of the patients, (100%) had scrotal pain and swelling; 88% of the patients had fever; 73% of the patients had been sweating.
- In 41 patients (69%) brucella species was isolated from their blood cultures and in 4 patients, brucella species was isolated from aspirates obtained from the epididymis.
- With regard to treatment, 39 patients had a combination of doxycycline and an aminoglycoside; 10 patients had doxycycline and rifampicin; 3 patients had trimethoprim-sulfamethoxazole with rifampicin; 7 patients had trimethoprim-sulfamethoxazole as monotherapy. The duration of treatment ranged between 21 days and 90 days with a median duration of 45 days.
- With regard to outcome, in 9 patients amounting to 15% of the patients the infection had failed to respond to treatment; 15 patients amounting to about 25% of the patients had experienced relapse of the disease; 3 patients who were diagnosed as having necrotizing orchitis and whose infections had not responded to antibiotic treatment had undergone orchiectomy. They had found out that generally classical brucellosis therapy was adequate for the treatment of brucella epididymoorchitis.
- Their review of the literature at the time of their publication had revealed complication rate of epididymoorchitis in 2% to 20% of patients with brucellosis; [23-29]; however, in their preliminary study the epididymoorchitis complicating brucellosis was 6% [24].
- A number of authors [17,18,21,23-25,30-34] had reported serious complications such as necrotizing orchitis associated with brucellosis orchitis and in view of this brucellosis orchitis should be considered in cases of acute scrotum in brucellosis endemic areas.
- At the time of their publication only few cases of genitourinary complications had been reported in the medical literature. [17, 18,23,24,30,31].

Akinci et al. [35] undertook a prospective study of patients afflicted by brucellosis between February 2001 and January 2004. They reported their results as follows:

- Epididymoorchitis was diagnosed in 17 out of 134 male patients (about 12.5%).
- The mean age of the patients was 36.9±7.1 years.
- The types of brucellosis which were diagnosed in the patients included twelve patients (70.6%) who had acute brucellosis, four patients (about 23.5%) who had sub-acute brucellosis and one patient (about 5.9%) who had chronic brucellosis.
- The commonest presenting symptoms were scrotal pain in 94% of patients and scrotal mass in 82% of the patients.
- Eleven patients had unilateral epididymoorchitis, four patients had unilateral orchitis, one patient had unilateral epididymitis, and testicular abscess was found in one patient.
- Fourteen of the patients had semen analysis and out of these, five had azospermia, and eight had oligospermia.
- With regard to treatment, the patients received combined antibiotic therapy for six to eight weeks; two patients underwent orchidectomy for which pathological examination revealed granulomatous orchitis in the excised specimens.
- With regard to the results of treatment, one patient experienced relapse, three patients had permanent oligospermia, one patient,

had permanent azospermia following the antibiotic therapy.
- They had also observed that younger age, high C reactive protein level and blood culture positivity were the statistically significant differences that were found between the patients who had epididymoorchitis and those who did not have epididymoorchitis.

Akinci et al. [35] made the ensuing conclusions:

- Brucellosis should be considered in the diagnosis of scrotal diseases in endemic areas.
- Usually, a conservative approach is sufficient in the management of brucella epididymoorchitis; nevertheless, the patients may develop problems of infertility.
- There is need for the development of well-designed further investigations to explain the relationship of brucella epididymoorchitis and infertility.

Al-Tawfiq [36] reported a forty-one year old man who presented with a history of fever, night sweats, and arthralgia as well as a left testicular swelling which was associated with pain. A few weeks prior to his presentation, he had ingested raw milk. On examination, his temperature was recorded as 39ºC and his systematic examination was normal. His left testis and his left epididymis were tender. The results of his laboratory tests were recorded as follows: White blood cell (WBC) count 5400 /mm^3, Blood culture was negative. Urinalysis revealed a white blood cell count of 0-5 per high power field (hpf) and red blood cell count of 10 to 25 per high power field. He had ultra-sound scan of testes and scrotal contents which showed an enlarged left testis with evidence of increased blood flow. It also showed that the left epididymis was enlarged with increased back shadowing which raised the possibility of early abscess formation (see Figs 1 and 2). His brucella abortus antibody titer was < 1:160 for IgG and > 1:2560 for IgM. A diagnosis of brucellosis epididymoorchitis was made and the patient was treated with doxycycline for six weeks as well as gentamicin for 2 weeks which resulted in complete resolution all his symptoms and signs. With regard to learning points, Al-Tawfiq [36] stated the following:

- Papatsoris et al. [37] had indicated that patients tend to present with acute symptoms of less than two weeks duration.
- Even though a number of patients may have epididymoorchitis or orchitis alone, bilateral bilateral epididymo-orchitis occurs in up to 59% of affected patients.
- Brucella epididymo-orchitis may be differentiated from non-specific epididymo-orchitis by means of history of contact with animals, consumption of raw milk or cheese made from it, gradual onset of symptoms, longer duration of symptoms, presentation with typical undulant fever, evidence of minimal local inflammation, absence of lower urinary tract symptoms and no evidence of significant leukocytosis.
- In brucellosis endemic areas suspicion of brucellosis epididymo-orchitis should be enough to start treatment for brucellosis whilst awaiting confirmatory results of laboratory tests.
- Urinalysis and urine culture reports had tended to be normal in majority of patients with brucellosis epididymo-orchitis (65%).
- Most of the patients who are diagnosed with brucellosis epididymo-orchitis tend to have initial agglutination titters of 1:320, 53% to 69%, tend to have positive blood cultures and 6.7% have positive culture from aspirates taken from the epididymis.
- Kocak et al. [12] had stated that brucellosis epididymo-ochitis may occur in the absence of systemic symptoms.
- Alapont Alacreu et al. [38] had iterated that the differentiation between brucellosis epididymo-orchitis and non-specific epididymo-orchitis is important in view of the fact that delay of specific treatment for brucellosis would increase the risk of contralateral involvement, necrosis as well as systemic manifestations.

Al-Tawfiq [36] advised that in brucelllosis endemic areas, brucellosis epididymo-orchitis should be considered in the differential diagnosis of patients who present with symptoms and signs of epididymo-orchitis.

Sevim et al. [6] reported a 38-year-old man who had been working in animal husbandry and whose work had involved production of milk and milk products. He had presented with fever, night sweats, chills, pain and tenderness in his testicles. On examination he was noted to be febrile with a temperature of 38.3 degrees centigrade. His right hemi-scrotum and right testis were noted to be increased in size (large). The right hemi-scrotum was red, warm, as well

as tender and furthermore. A provisional diagnosis of epididymo-orchitis was made and the patient was started on ciprofloxacin 500 mg twice per day as well as dexketoprofen 25 mg twice per day and he was asked to come for follow-up. He had to be admitted 5 days later because of persisting symptoms. The results of his laboratory tests were reported as follows: leucocyte count 10000 /mm^3 (81.4% polymer-phonuclear leucocytes, 13.5% lymphocytes, and 4.9% monocytes, 0.2% basophils), erythrocyte sedimentation rate 20 mm/hour, reactive Protein 18 mg/l, aspartate aminotransferase 23/l, alanine aminotransferase, 33.4 U/L, Rose Bengal test positive, Wright agglutination test 1/640 titer which was regarded as positive. He had Doppler ultrasound scan of scrotal contents which revealed the right testicular parenchymal echogenicity to be heterogeneous and within the mid lower part of the right testis hypo-echoic areas which measured 33 mm x 22 mm in size which was reported to be consistent with epididymo-orchitis. Based upon the afore-mentioned findings, a diagnosis of brucellosis epididymo-orchitis was made. The patient was treated by means of: scrotal elevation, local cold compress, rifampicin 600 mg three times a day for six weeks plus doxycycline 200 mg per day for six weeks plus streptomycin 1 gr/g's for two weeks and nonsteroidal anti-inflammatory therapy. By the 4^{th} day there was evidence of clinical improvement in that his systemic symptoms and his right hemi-scrotal hyperaemia had disappeared. His testicular pain and swelling had reduced and he was discharged. At his 2^{nd} follow-up 15 days after his treatment was started, all his symptoms had completely disappeared. But in order to prevent relapse he was advised to complete a six weeks course of both rifampicin 600 mg per day and doxycycline 200 mg per day as well as to return for further follow-up.

Ibrahim et al. [23] presented 12 cases of genito-urinary complications of brucellosis. They reported that ten of the patients had presented with epididymo-orchitis, one patient presented with right hydronephrosis, and another patient presented with haematuria and dysuria. Ibrahim et al. [23] compared the ten cases of epididymo-orchitis with 15 cases of acute non-specific epididymo-orchitis and they stated the following:

- The ten cases of brucella epididymo-orchitis were of longer duration and they did not have any lower urinary tract symptoms; almost all the patients in this group had ingested unpasteurized milk.
- Non-specific epididymo-orchitis on the other hand had a more acute onset, shorter duration, and was associated more often with pyuria, lower urinary tract symptoms, higher leucocyte counts and insignificant brucella titers.
- The differentiation between the two different types of epididymo-orchitis is essential in view of the fact that the treatments are different for the two groups.

Colmenero et al. [26] undertook a prospective study of 530 patients older than 14 years who had been afflicted with brucellosis. They reported the following:

- One hundred and sixty-nine patients (31.9%) had a focal form or complication. Osteoarticular complications were the most common, which totaled 113 cases (66%). This was followed by genito-urinary complications with 18 cases and this amounted to 5.1% of males. Hepatic complications amounted to 2.5% of cases. Neurologic and heart complications amounted to 1.7% and 1.5% of cases respectively. Nine patients (1.7%) had more than one complication.
- Multivariate analysis revealed that diagnostic delay greater than 30 days (OR 2.0), ESR >40 mm/hr (OR > 1.9), and levels of alpha-2 globulins greater than 7.5 grams / liter (OR 6.8) were statistically significant independent variables associated with presence of focal forms.
- Twenty five patients with complications (14.8%) underwent surgical treatment.
- The relapse rate was 3.6% in cases of those patients who did not have complications and the relapse rate was 4.1% for the patients who had focal forms ($P>0.05$). Nevertheless, when the therapeutic failure, relapses, and mortality were considered together, the risk of an unfavorable evolution was found to be significantly greater in patients who had focal forms of the disease (10.6% in comparison with 3.6% in patients who did not have any complications; OR 1.9, 95% CI 1.4 – 4.71, $P < 0.005$).

They concluded that with regard to the worse prognosis, knowledge and early diagnosis of brucellosis melitensis infection is especially important.

Afsar et al. [27] reported on 13 patients who were diagnosed with brucellosis epididymo-orchitis between 1989 and 1991. They reported that both the testis and epididymis was involved in 8 patients, 3 had bilateral epididymo-orchitis, and 2 presented with orchitis alone. The patients were treated with 200 mg of doxycycline daily for six weeks and rifampicin 600 mg daily for six weeks. With regard to the outcome of treatment, 10 patients had complete resolution.

Quelpo Ortuno et al. [39] studied the diagnostic yield of real-time polymerase chain reaction (PCR) assay in urine samples for the rapid diagnosis of brucella epididymo-orchitis compared to that of conventional microbiological techniques. Quelpo Ortuno et al. [39] used SYBR® Green I Light Cycler® based real-time polymerase chain to retrospectively study 10 urine samples which had been obtained from patients who had been afflicted with brucellosis epididymo-orchitis. The assay does amplify a 223 bp sequence of a gene which codes for the synthesis of an immunogenic membrane protein specific for Brucella genus (BCSP31). Quelpo Ortuno et al. [39] stated that after they had amplified the 223 bp sequence they performed melting curve analysis to verify the specificity of polymerase chain reaction products. Quelpo Ortuno et al. [39] reported that:

- They had isolated brucella mellitensis from blood cultures in 9 cases (90%).
- Wright's seroagglutination was negative or not conclusive in 30% of the cases.
- They had isolated brucella from urine in only one case; on the other hand, real-time polymerase chain reaction assay in urine was positive in 9 cases (90%). Furthermore, the results were available in 4 hours, whereas the mean time to the availability of the final blood culture results was 5.8 days with a range of 4.5 days to 7 days.

Quelpo Ortuno et al. [39] concluded that (a) real-time polymerase chain reaction (PCR) assay in urine samples is highly sensitive and specific and easy to perform; (b) real-time polymerase chain reaction (PCR) assay in urine samples could provide clinicians with the results in less than 5 hours; (c) the technique could be a practical and useful tool for the rapid diagnosis of genitourinary complications of human brucellosis.

Yurdakul et al. [30] reported a study of 84 patients who had been diagnosed with epididymo-orchitis between July 1987 and September 1993. They reported that brucellosis was a complication in 14 cases (17%); all 14 cases had elevated agglutination titers; they found brucella blood culture to be positive in 4 (28.5%) out of the 14 cases; standard therapy regimen which consisted of streptomycin and tetracycline was effective in13 of 14 (93%) cases.

Khan et al. [18] reported a series of 40 patients who were diagnosed with epididymo-orchitis between January 1983 and August 1985. They reported that in 14 of the cases brucellosis was diagnosed and in 10 of the 14 cases both the testis and epididymis were involved and 1 patient had bilateral disease. All the 14 patients who had brucella epididymoorchitis were treated with streptomycin and tetracycline and 8 patients (57%) experienced complete resolution.

Gul et al. [40] reported on 19 patients who were diagnosed with epididymo-orchitis due to brucella melitensis between 1998 and 2005 in their hospital. They stated that the diagnosis of brucella epididymitis was made by isolating brucella species from blood culture or epididymal aspirations or by standard tube agglutination testing and slide agglutination testing together with clinical findings. They reported that seven cases (36.8%) had undulant fever. Brucella species was isolated from blood cultures in 11 patients and from epididymal aspirations in 3 patients. Rose Bengal tests were positive in all of the patients. Total recovery was achieved in 12 patients with a 6-week treatment. Five patients (26.3%) did not respond to therapy and another 2 (10.5%) had relapsed. Gul et al. [40] concluded that in brucella endemic areas, Brucella orchitis should be considered in the differential diagnosis of scrotal pathologies.

Naiafi et al. [41] reported a retrospective study in which they had identified 30 cases of brucella epididymitis in two hospitals in north of Iran between 1997 and 2009. They reported that epididymo-orchitis occurred in 11.1% of male patients with brucellosis. The average age was 22.5 ± 12.43 years. The commonest symptoms were pain and scrotal swelling which occurred in all the cases (100%) and fever occurred in 96.7% of the patients. Different treatment regimens were given including doxycycline plus rifampin in 60% of the cases, doxycycline plus rifampin plus aminoglycoside for the first two weeks (36.6%) and doxycycline plus cotrimoxazole were given in 3.4% of the patients. Ten percent of the patients

did not respond to antibiotic therapy and they required surgical drainage or orchiectomy. Naiafi et al. [41] concluded that: In brucellosis endemic areas clinicians who encounter patients with epididymo-orchitis should take into consideration the likelihood of brucellosis. A careful history taking and physical examination as well as immediate laboratory examination would help in establishing a correct diagnosis. Generally, classical therapy of brucellosis is adequate for the treatment of epididymo-orchitis.

4. CONCLUSIONS

Clinicians should be aware that brucellosis epididymo-orchitis, brucellosis epididymitis and epididimo-orchitis exist and this condition could be unilateral or bilateral, though more commonly encountered in brucellosis endemic areas because of global travel the disease entity may be encountered sporadically globally.

Brucellosis epididymo-orchitis should be considered as a differential diagnosis when patients present with symptoms and signs suggestive of non-specific epididymo-orchitis, orchitis or epididymitis.

Brucellosis epididymo-orchitis tends to have a good outcome when appropriate standard combination antibiotic treatment is given early.

Duration of appropriate combination treatment given in BEO had varied from 21 days to 90 days but in majority of cases duration of treatment had been around six weeks to 45 days. An average of six weeks to 45 days treatment would be sufficient in most cases. Nevertheless, duration of treatment should be continued until there is clinical evidence of resolution of the BEO in addition to return of Brucellosis serological titers to normal and radiological evidence of resolution of BEO which may make the duration of treatment last longer than 6 weeks and may be prolonged up to about 90 days.

Two-drug antibiotic regimen has been effective in the treatment of most cases of BEO; however, there is information to suggest that triple-antibiotic therapy may be more effective without treatment failure and may be associated with no evidence of relapse or very lot rate of relapse in comparison with 2-drug antibiotic therapy.

Inappropriate management and or delay in diagnosis and delay in initiating appropriate combination antibiotic treatment may lead to serious complications including testicular abscess, testicular atrophy and infertility.

Occasionally because of the fact that brucellosis testicular and epididymal lesions cannot be completely differentiated from testicular tumours, orchidectomies had been undertaken as treatment following which the diagnosis was established.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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