Chapter 12

Treatment of Human Brucellosis — Review of Evidence from Clinical Trials

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Abstract

Unresolved issues remain surrounding the treatment of human brucellosis. The present work aims to provide useful information to help clinicians make decisions when treating brucellosis patients. Information based on scientific evidence from clinical trials published over the past 30 years has been compiled and presented in an updated form, covering both focal and non-focal, or uncomplicated, human brucellosis. This chapter shows that, despite the studies published in recent years, areas such as the role of monotherapy or treatment in cases of focal disease, have not been adequately addressed in clinical trials, and demonstrates the need for further research.

Keywords: Human brucellosis, antimicrobial therapy, clinical trials, review

1. Introduction

Infection caused by *Brucella spp.* affects humans and different animal species. The infection of animals is particularly significant in rural areas of developing countries because in addition to the implications for human health, there are also serious economic implications [1]. Human brucellosis remains a major human health problem in countries of the Middle East, North Africa, and the Balkan Peninsula [2, 3]. Many of these countries lack adequate health care coverage that can ensure a correct management of all detected cases.

Furthermore, the treatment of human brucellosis continues to present complications such as the need for parenteral administration of aminoglycosides, the risk of inducing rifampicin resistance in countries where tuberculosis poses a problem, and treatment compliance in a disease in which symptoms disappear a few days after initiating therapy. Additionally, patient follow-up in underdeveloped rural areas is difficult and approximately 10% of patients relapse

[4]. Moreover, there is insufficient scientific evidence on the management of special patient groups such as pregnant women or patients with focal infection.

In order to properly understand the current state of knowledge on antimicrobial treatment for human brucellosis, it is important to be familiar with the clinical trials conducted on the treatment of this infection, including those dealing with special populations (children, pregnant women) or with focal complications (spondylitis, endocarditis, or neurobrucellosis).

In the last four years, several systematic reviews [4-6] and some new clinical trials [7-9] have been published. Most of these studies have focused on patients with uncomplicated human brucellosis. The present work aims to provide useful information extracted from published clinical trials on human brucellosis in the past 30 years, such as establishing the most effective evidence-based treatment regimens and identifying those treatment issues that remain unclear or insufficiently addressed. This is an important step toward achieving the goal of aiding clinicians in decision-making processes when treating brucellosis patients.

2. Which treatment regimens were most widely tested in clinical trials?

A search for clinical trials in patients with acute brucellosis published in the last 30 years was conducted in MEDLINE, using the terms "Brucella (or human brucellosis) and therapy (or treatment) and clinical trial." A total of 33 comparative clinical trials were found. The search was completed by the literature cited in these clinical studies.

Interest in this topic is also reflected by the fact that in the last 20 years, there have been at least five systematic reviews on the treatment of uncomplicated human brucellosis [4-6, 10, 11]. These reviews help us to summarize the evidence available to date. Table 1 shows the comparative clinical trials conducted on patients with uncomplicated brucellosis. [COMP: insert Table 1]

Author [Ref]	Year	Country	Therapeutic regimen and duration (days)	Follow-up duration (months)	Type of study
Ariza [12]	1985	Spain	TETR ó DX (30) + STP (21) vs DX (30) + RF (30)	6-24	R
Ariza [34]	1985	Spain	TETR (21) + STP (14) vs TMP/SMX (45)	6-36	R
Colmenero [13]	1989	Spain	DX (30) + STP (21) vs DX (45) + RF (45)	6	R
Acocella [14]	1989	Multinational	TETR (21) + STP (14) vs DX (45) + STP (14) vs DX (45) + RF (45)	12	R
Lang [15]	1990	Israel	CPX (42) vs DX (42) + RF (42)	12	R
Solera [16]	1991	Spain	DX (45) + STP (14) vs DX (45) + RF (45)	12	R
Lang [31]	1992	Israel	Ceftriaxone (≥14) vs DX (28) + STP (14)	6	R
Ariza [17]	1992	Spain	DX (45) + STP (15) vs DX (45) + RF (45)	15.7	R, DB

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Author [Ref]	Year	Country	Therapeutic regimen and duration (days)	Follow-up duration (months)	Type of study
Montejo [18]	1993	Spain	DX (42) + STP (14) vs DX (42) + STP (21) vs DX (28) + RF (28) vs DX (42) + RF (42) vs DX (42) vs TMP/SMX (180)	12	R
Akova [19]	1993	Turkey	DX (42) + RF (42) vs OFX (42) + RF (42)	14.6	R
Colmenero [20]	1994	Spain	DX (42) + STP (21) vs DX (42) + RF (42)	6	R
Solera [21]	1995	Spain	DX (45) + STP (14) vs DX (45) + RF (45)	12	R
Kalo [22]	1996	Albania	DX (42) + RF (42) vs DX (42) + CPX (42)	6	R
Solera [42]	1997	Spain	DX (30) + G (7) vs DX (45) + G (7)	12	NR
Agalar [23]	1999	Turkey	DX (45) + RF (45) vs CPX (30) + RF (30)	12	R
Saltoglu [24]	2002	Turkey	DX (45) + RF(45) vs OFX (45) + RF (45)	6	R
Karabay [25]	2004	Turkey	DX (45) + RF (45) vs OFX (30) + RF (30)	~5	R
Hasanjani Roushan [43]	2004	Iran	TMP/SMX (60) + RF (60) vs DX (60) + TMP/SMX (60)	12	R
Solera [44]	2004	Spain	DX (30) + G (7) vs DX (45) + G (7)	8.7	R, DB
Ersoy [26]	2005	Turkey	DX (42) + STP (21) vs DX (42) + RF (42) vs OFX (42) + RF (42)	6-18	R
Hasanjani Roushan [32]	2006	Iran	DX (45) + STP (14) vs DX (45) + G (7)	12	R
Ranjbar [27]	2007	Iran	DX (56-84) + RF (56-84) + AMK (7) vs DX (56) + RF (56)	6	R
Alavi [28]	2007	Iran	DX (56) + RF (56) vs DX (56) + TMP/SMX (56)	6	R
Keramat [29]	2009	Iran	DX (56-84) + RF (56-84) vs DX (56-84) + CPX (56-84) vs CPX (56-84) + RF (56-84)	6	R
Hasanjani Roushan [33]	2010	Iran	DX (45) + STP (14) vs DX (56) + G (5)	12	R
Mile [7]	2012	Macedonia	DX (45) + RF (45) vs DX (45) + RF (45) + G (7-10)	≥6	NR
Hashemi [30]	2012	Iran	OFX (42) + RF (42) vs DX (42) + STP (21) vs DX (42) + RF (42)	6	R
Sofian [9]	2014	Iran	DX (42) + RF (42) + STP (7) vs DX (56) +RF (56) + STP (7)	24	R

Abbreviations: DX = doxycycline; RF = rifampicin; TETR = tetracycline; STP = streptomycin; TMP/SMX = cotrimoxazole; CPX = ciprofloxacin; OFX = ofloxacin; G = gentamicin; AMK = amikacin; R = randomized; NR = non-randomized; DB = double-blind.

Table 1. Comparative clinical trials in uncomplicated human brucellosis

The therapeutic regimens most tested were those including two drugs. In uncomplicated human brucellosis, the combination most often used in two-drug trials was that of doxycycline and rifampicin, included in 20 clinical trials [7, 12-30], followed by the regimen including doxycycline and streptomycin, in 13 clinical trials [12-14, 16-18, 20, 21, 26, 30-33]. In 12 of these 13 trials, the combination of doxycycline and streptomycin was compared to the combination of doxycycline and rifampicin. In another nine clinical trials, an antimicrobial regimen including quinolones was tested [15, 19, 22-26, 29, 30]. In one of them, quinolone was evaluated as monotherapy [15] and in the other eight, quinolone in combination with another antimicrobial agent, usually rifampicin. In all cases in which quinolones were used, they were compared with doxycycline and rifampicin.

There were only three trials including triple-drug therapy [7, 9, 27], which in all cases consisted of a combination of doxycycline, rifampicin, and an aminoglycoside. In two of these studies, triple-drug therapy was compared with doxycycline and rifampicin. In the remaining study, two different durations of the same triple-drug therapy were compared.

Four studies included trials with only a single antimicrobial agent. One trial was performed using ceftriaxone [31] and another one using ciprofloxacin [15]. In another two, the antimicrobial agent evaluated was cotrimoxazole [18, 34]. Only one clinical trial utilizing monotherapy with doxycycline has been conducted over the last 30 years [18]. The last study involving monotherapy was published by Montejo et al. in 1993 [18]. Since then, there have been no clinical trials conducted on human brucellosis assessing treatment with single antimicrobial agents.

3. Which therapeutic regimens based on a combination of two antimicrobial agents produced the highest cure rates?

The percentage of relapses and treatment failures obtained in clinical trials assessing the most commonly used regimens, are shown in Table 2. The data in Table 2 support the conclusion that the combination of doxycycline and streptomycin produces the highest cure rates and therefore the lowest rates of treatment failures and relapses. [COMP: insert Table 2]

Reference	*N*	Relapses	Therapeutic failures	Comments
DOXYCYCLINE + STREPTOMYCIN				
12	28	2	0	Some patients were treated with tetracycline. Treatment duration was 30 days for doxycycline and 21 days for streptomycin.
14	53	0	2	
13	59	3	2	Treatment duration was 30 days for doxycycline and 21 days for streptomycin.

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Reference	*N*	Relapses	Therapeutic failures	Comments
16	38	2	1	
31	10	0	0	Treatment duration was 28 days for doxycycline and 14 days for streptomycin..
17	51	3	2	
18	84	4	0	40 patients with 14 days of streptomycin and another 44 patients with 21 days of streptomycin were included.
20	10	0	0	
21	94	5	2	
26	32	3	1	Treatment with streptomycin was maintained for 21 days.
32	94	3	4	
33	82	5	4	
30	65	3	3	Treatment with streptomycin was maintained for 21 days.
Total	839	37 (4.4%)	26 (3.1%)	
			DOXYCYCLINE + RIFAMPICIN	
12	18	7	0	The treatment duration was 30 days.
13	52	7	0	
14	63	3	0	
15	4	0	0	
16	38	9	3	
17	44	6	2	
18	111	19	2	65 of these patients received treatment for 4 weeks and the remaining patients for 6 weeks.
19	30	1	0	
20	10	1	1	
21	100	16	8	
22	12	1	0	
23	20	2	0	
24	30	2	NR	
25	14	2	0	
26	45	6	1	
27	110	9	13	Treatment was maintained for 8 weeks.
28	51	6	5	Treatment was maintained for 8 weeks.
29	61	2	2	
7	94	13	5	
30	62	9	10	
Total	969	121 (21.8%)	52 (5.4%)	

Reference	*N*	Relapses	Therapeutic failures	Comments
QUINOLONE + RIFAMPICIN ÓR DOXYCYCLINE				
19	31	1	1	Quinolone + rifampicin
22	12	1	0	Quinolone + doxycycline
23	20	3	0	Quinolone + rifampicin. Treatment duration was 30 days.
24	27	2	NR	Quinolone + rifampicin
25	15	2	0	Quinolone + rifampicin. Treatment duration was 30 days.
26	41	5	1	Quinolone + rifampicin
29	117	10	10	In 55 patients, ciprofloxacin plus doxycycline regimen was used. In another 62 patients, ciprofloxacin plus rifampicin regimen was used. The treatment duration ranged from 56 to 84 days.
30	64	5	4	Quinolone + rifampicin
Total	327	29 (8.9%)	16 (4.9%)	

Table 2. Relapses and treatment failures in different therapeutic regimens used in clinical trials

4. Is triple-drug antimicrobial therapy better than the combination of two antimicrobial agents for the treatment of uncomplicated brucellosis?

Only three clinical trials using a triple-drug antimicrobial therapy for the treatment of uncomplicated human brucellosis have been published (Table 3). All these trials used a combination of doxycycline, rifampicin, and an aminoglycoside during the initial days of treatment. [COMP: insert Table 3]

The first of these trials was published by Ranjbar et al. in 2007 [27]. In this trial, a treatment regimen with doxycycline and rifampicin was used for a period ranging from 8 to 12 weeks, with amikacin for the first seven days. This regimen was compared to a combination of doxycycline and rifampicin, also lasting for 8-12 weeks. The authors suggested that triple-drug therapy was beneficial with respect to the dual-drug therapy, based on greater efficiency in terms of relief of symptoms, with borderline significance ($p = 0.04$; 95% Confidence Interval = 0.008 to 0.15). In terms of relapse, no significant differences between the two treatment groups ($p = 0.4$) were obtained.

The second trial was conducted by Mile et al. [7]. It was a non-randomized study comparing the efficacy and tolerance of a doxycycline-rifampicin regimen administered for 45 days (94 patients), versus doxycycline-rifampicin regimen given for 45 days plus gentamicin for the first 7-10 days (87 patients). The doxycycline-rifampicin-gentamicin regimen demonstrated a significantly lower relapse rate in comparison to the doxycycline-rifampicin combination ($p = 0.034$). Interestingly, in this second study, treatment failure rates were similar in both groups and no significant differences were found in overall cure rate ($p = 0.097$).

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Reference	*N*	Relapses	Treatment failures	Comments
DOXYCYCLINE + RIFAMPICIN + AMINOGLYCOSIDE				
27	110	6	4	The duration of treatment ranged from 8 to 12 weeks. The aminoglycoside amikacin was used for 7 days.
7	87	4	5	The treatment duration was 45 days. The aminoglycoside gentamicin was used for the first 7-10 days.
9	72	10	0	The treatment duration was 6 weeks. The aminoglycoside streptomycin was used for the first 7 days.
9	72	7	0	The treatment duration was 8 weeks. The aminoglycoside streptomycin was used for the first 7 days.
Total	341	27 (7.9%)	9 (2.6%)	

Table 3. Relapses and treatment failures with triple-drug therapy in clinical trials on human brucellosis

The third study was published in 2014 by Sofian et al. [9]. It was a randomized, controlled trial to compare the triple-drug regimen of doxycycline and rifampicin for six weeks plus streptomycin for the first seven days, versus doxycycline and rifampicin for eight weeks plus streptomycin for seven days. This trial found no significant difference between six weeks and eight weeks of treatment ($p = 0.42$).

On the basis of these trials, it cannot be concluded that treatment with three drugs is currently a better therapeutic regimen than treatment with two drugs. There are several arguments to support this conclusion. Firstly, only two of these trials compared triple-drug therapy with dual-drug therapy, and the results between these two trials were contradictory. Whereas in the first trial, triple-drug therapy was better in terms of relief of symptoms but not in terms of relapse rates, in the second trial, the contrary occurs, with triple-drug therapy more effective in preventing relapses but not in short-term treatment success. Moreover, failure and relapse rates obtained in these trials with triple-drug therapy were no lower than those obtained in other dual-drug therapy trials using doxycycline and streptomycin (Tables 2 and 3). Furthermore, triple-drug therapy renders treatment more complicated, with increased costs. In addition, the effects resulting from the difficulty of administering this treatment in developing countries should also be considered [4]. Therefore, until more data are available, we cannot conclude that triple-drug therapy is better than two-drug treatment.

5. Is monotherapy a valid alternative?

Human brucellosis is a disease with low mortality rates and good response to different therapeutic regimens. Most cases occur in developing countries with limited resources. This fact has led some authors to consider the use of more simple and inexpensive therapeutic regimens based on monotherapy.

Only four of the studies included in Table 1 tested therapeutic regimens based on monotherapy in uncomplicated adult human brucellosis. Monotherapy with cotrimoxazole for 45 days was evaluated by Ariza et al., and they obtained a high relapse rate (46.6%) [34]. Montejo et al. were

able to reduce the recurrence rate with cotrimoxazole to 3.1%, but at the cost of prolonging the treatment for 6 months [18], which also increases the probability of side effects or of the patient's abandonment of treatment.

Lang et al. performed two monotherapy trials with a small number of patients. In the first of these trials, six patients treated with a six-week regimen of oral ciprofloxacin were included [15]. Of these patients, five relapsed. In the second clinical trial, eight patients were treated with intramuscular ceftriaxone for at least two weeks [31]. Only two patients in this group responded to treatment.

However, unlike in the previously described trials, in the study conducted by Montejo et al. [18], the results obtained with doxycycline monotherapy were better, showing a relapse rate of 14.1%, which was only slightly higher than that obtained in the same study with the combination of doxycycline and rifampicin for 45 days (11%). These results were also better than those obtained with rifampicin and doxycycline for 30 days (21.5% relapse rate). Doxycycline monotherapy appears to yield similar outcomes to those obtained by some of the trials using both doxycycline and rifampicin that are reflected in Table 2.

Therefore, it has been postulated that monotherapy with doxycycline can be a cost-effective treatment in patients without focal disease and with low risk of relapse. Solera et al. [35] identified as predictors of relapse a baseline temperature more than 38.3°C, duration of symptoms to be less than 10 days before starting the treatment, and baseline positive blood cultures. In patients with none or one of these factors, the risk of recurrence is low, and doxycycline monotherapy might be an appropriate treatment. Further clinical trials are needed to confirm this hypothesis.

6. Which treatment regimens were used in clinical trials on brucellosis in children?

There were three trials conducted in children with brucellosis. Firstly, the trial by Lubani et al. [36] was performed using a variety of therapeutic regimens. Excluding cotrimoxazole monotherapy, which showed a high rate of relapse (30%), the rest of the treatment regimens in the study (including monotherapy regimens) demonstrated good results with low relapse and treatment failure rates. The authors of this trial recommend cotrimoxazole and gentamicin-containing regimens for patients aged 8 years or younger, for whom tetracyclines are contraindicated.

Khuri-Bulos et al. [37] conducted a study in which 113 children were treated with a six-week combination of trimethoprim-sulfamethoxazole (10 to 12 mg/kg trimethoprim, 50 to 60 mg/kg sulfamethoxazole) and rifampicin (15 to 20 mg/kg in two divided doses). The treatment was well-tolerated, and only four children relapsed during the six-month follow-up.

Hasanjani Roushan et al. [38] published a study on two different durations for a regimen including cotrimoxazole and rifampicin (42 versus 56 days of treatment). After a year of follow-up, the authors observed a similar cure rate in the two treatment groups (89.1% and 95.5% cure

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rate for 42 and 56 days, respectively; $p = 0.204$). The authors reached the conclusion that a six-week treatment duration was sufficient to treat brucellosis.

Considering these data, it can be stated that childhood brucellosis responds to treatment regimens that include cotrimoxazole, gentamicin, and rifampicin, with a low failure rate and relapse. Although recommended regimens are those including cotrimoxazole or rifampicin for 45 days plus gentamicin in the first seven days [1], clinical trials also showed a good treatment response rate to cotrimoxazole plus rifampicin for six weeks.

7. Which treatment regimens were used in clinical trials for the treatment of brucella spondylitis?

There were two clinical trials on patients with brucellar spondylitis. The first was performed by Bayindir et al. [39]. In this study, 102 patients suffering from a lumbar brucellar spondylitis were randomized to receive five different regimens of antibiotic therapy: streptomycin (15 days) plus tetracycline (45 days), doxycycline (45 days) plus streptomycin (15 days), doxycycline plus rifampicin (45 days), ofloxacin plus rifampicin (45 days), and finally doxycycline plus rifampicin (45 days) plus streptomycin (15 days). The only group in which there were no relapses or treatment failures was the one that received triple-drug therapy with doxycycline, rifampicin, and streptomycin. Thus, this treatment was recommended by the study authors according to their results.

The other trial, conducted by Alp et al. [40], included 31 patients with spinal brucellosis who were consecutively assigned to one of two treatment regimens tested. These treatments were either a combination of doxycycline and streptomycin, or a combination of ciprofloxacin with rifampicin. Treatment was continued for an average of 12 weeks. The authors concluded that the success rate with each combination was the same, but based on the lower cost of treatment, the authors recommended the combination of streptomycin and doxycycline.

According to these two trials, it may be concluded that triple-drug therapy successfully treats brucellar spondylitis with a short course of just 45 days of antibiotics versus dual-drug therapy. However, despite the greater methodological difficulties of the second trial described here, therapy with doxycycline and streptomycin could be an alternative if treatment time is prolonged.

8. Which treatment regimens were used in clinical trials on brucellosis in pregnancy?

No clinical trials on the treatment of brucellosis during pregnancy were found. Therefore, the therapy in this group of patients is mainly based on expert recommendations and observational studies. Tetracycline and streptomycin should be avoided during pregnancy. The regimen of choice includes rifampicin 900 mg daily for six weeks. Trimethoprim-sulfamethoxazole

could be combined with rifampicin, but should not be used before 13 weeks of pregnancy because of teratogenic risk nor after 36 weeks due to risk of kernicterus [1, 3].

9. Which treatment regimens were used in clinical trials for the treatment of Brucella endocarditis?

Likewise, no clinical studies were found on patients suffering from Brucella endocarditis and, as with brucellosis during pregnancy, the therapy in this group of patients is mainly based on expert recommendations and observational studies. Antibiotics used in these cases include doxycycline, rifampicin, and aminoglycosides in triple-drug therapy and sometimes cotrimoxazole [1, 3]. Brucella endocarditis requires prolonged treatment for 2 to 10 months and must be maintained on the basis of clinical, laboratory, and echocardiographic data. In cases of persistent infection, prosthetic valve infection, heart failure, abscesses or periannular extension of infection, surgery is indicated [3].

10. Which treatment regimens were used in clinical trials for the treatment of neurobrucellosis?

Involvement of the nervous system in Brucella infection may have different manifestations such as meningoencephalitis, myelitis, radiculitis, peripheral neuropathies, subarachnoid hemorrhage, or psychiatric manifestations [41]. There is no consensus on antibiotic therapy for neurobrucellosis. No clinical trials on patients suffering from neurobrucellosis have been found. Dual- or triple-combination therapy with doxycycline, rifampicin, trimethoprim-sulfamethoxazole, and aminoglycosides has been recommended [3, 41]. Neurobrucellosis may require prolonged courses of treatment over several months.

11. What systematic reviews have been conducted on the treatment of human brucellosis?

Until now, five systematic reviews on the treatment of human brucellosis have been conducted [4-6, 10, 11] (Table 4). The first was published in 1997 and was performed with the aim of comparing a doxycycline plus streptomycin regimen with a doxycycline plus rifampicin regimen [10]. The authors concluded that the doxycycline-rifampicin treatment presented a greater number of relapses and a lower number of cures than streptomycin-doxycycline treatment.

The next published systematic review was performed by Skalski et al. [11], which recommended triple-drug therapy as one of the most appropriate regimens. However, as indicated by Yousefi-Nooraie et al. [5], the review had some methodological limitations, such as

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combining trials based on different drug classes (e.g., comparing quinolone with non-quinolone-based regimens) or comparing studies on brucellar spondylitis with studies on non-complicated brucellosis, despite differences in the treatment duration of these studies.

Since then, three other systematic reviews have been published [4-6]. Despite some differences in the methodology used among the three, the conclusion they all reached was that the combination of doxycycline-aminoglycoside [especially doxycycline (six weeks) plus streptomycin (two or three weeks)] in uncomplicated adult brucellosis was more effective than a doxycycline plus rifampicin (six-week) regimen.

Author [Ref]	Year	Conclusions
Solera [10]	1994	"In human brucellosis, treatment with rifampicin and doxycycline presents a greater number of recurrences and a lower number of cures than the classical treatment with streptomycin and tetracycline drugs."
Skalsky [11]	2008	"There are significant differences in effectiveness between currently recommended treatment regimens for brucellosis. The preferred treatment should be with dual or triple regimens including an aminoglycoside."
Solís García del Pozo [4]	2012	"Although the preferred treatment in uncomplicated human brucellosis is a doxycycline-aminoglycoside combination, other treatments based on oral regimens or monotherapy should not be rejected until they are better studied. Triple therapy should not be considered the current treatment of choice."
Yousefi-Nooraie [5]	2012	"A doxycycline (six weeks) plus streptomycin (two or three weeks) regimen is more effective than a doxycycline plus rifampicin (six weeks) regimen. Quinolone plus rifampicin (six weeks) is slightly better tolerated than doxycycline plus rifampicin, and low quality evidence did not show any difference in overall effectiveness."
Alavi [6]	2013	"In uncomplicated brucellosis in adult patients, a doxycycline-aminoglycoside combination is the first choice, with doxycycline-rifampin and doxycycline-cotrimoxazole as alternative regimens. The other oral regimens including quinolones may be considered as alternatives. Cotrimoxazole plus rifampin for six weeks may be the regimen of choice for the treatment of patients younger than 8 years old. Gentamicin for 5 days plus cotrimoxazole for six weeks may be a suitable alternative regimen."

Table 4. Main conclusions of the systematic reviews published on treatment of human brucellosis

12. Conclusions

Over the past few years, several trials and systematic reviews on the treatment of human brucellosis have been published. However, unresolved issues remain surrounding the

treatment of this disease that may be important for patient management, such as the role of monotherapy in low risk patients, or treatment for special groups such as those with focal disease. These unresolved issues have not been adequately addressed in clinical trials. Further research on the treatment of this zoonosis is necessary to provide the clinician with the best scientific evidence upon which to base clinical decisions.

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