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Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objectives To determine and quantify differences in efficacy between treatment regimens for brucellosis.

Design Systematic review and meta-analysis of randomised controlled trials assessing different antibiotic regimens and durations of treatment for human brucellosis.

Data sources PubMed, CENTRAL, Lilacs, conference proceedings, and bibliographies with no restrictions on language, study year, or publication status.

Review methods Search, application of inclusion and exclusion criteria, data extraction, and assessment of methodological quality independently performed in duplicate. Primary outcomes were relapse and overall failure resulting from primary failure or relapse. Relative risks with 95% confidence intervals were calculated and pooled with a fixed effect model.

Results 30 trials and 77 treatment arms were included. Overall failure was significantly higher with doxycycline-rifampicin compared to doxycycline-streptomycin, mainly due to a higher rate of relapse (relative risk 2.80, 95% confidence interval 1.81 to 4.36; 13 trials, without heterogeneity). Results were consistent among patients with bacteraemia and complicated brucellosis.

Doxycycline-streptomycin resulted in a significantly higher rate of failure than doxycycline-rifampicin-aminoglycoside (triple drug regimen) (2.50, 1.26 to 5.00; two trials). Gentamicin was not inferior to streptomycin (1.45, 0.52 to 4.00 for failure; two trials). Quinolones combined with rifampicin were significantly less effective than doxycycline combined with rifampicin or streptomycin (1.83, 1.11 to 3.02, for failure; five trials). Monotherapy was associated with a higher risk of failure than combined treatment when administered for a similar duration (2.56, 1.55 to 4.23; five trials). Treatment for six

weeks or more offered an advantage over shorter treatment durations.

Conclusions 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.

INTRODUCTION

Brucellosis is the commonest zoonotic infection worldwide. Treatment is given to shorten the duration of symptoms, prevent relapse, and avert complications. Recommendations for specific regimens are inconsistent. Guidelines of the World Health Organization, last published in 1986, recommend doxycycline with rifampicin for six weeks in place of their previously recommended regimen of tetracycline for six weeks in combination with streptomycin for the first two to three weeks.¹ The relative merits of these two regimens are still being discussed.²⁻⁵ Recent consensus recommendations of an expert panel proposed doxycycline-streptomycin and doxycycline-rifampicin as first line regimens, without quantifying the differences between them.⁶

We performed a systematic review and meta-analysis of all randomised controlled trials that assessed different antibiotic regimens for the treatment of brucellosis to identify the optimal treatment regimen and duration of treatment and to obtain quantitative estimates of effect for the difference between existing regimens.

METHODS

We included randomised or quasi-randomised controlled trials that tested any single or combination

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antibiotic treatment for *Brucella* infections compared with placebo, no treatment, or another antibiotic regimen. We included trials in adults or children with documented infections caused by *Brucella* spp.

Our four predefined comparisons were any tetracycline combined with any aminoglycoside versus any tetracycline combined with rifampicin or its derivatives; combination regimens with a quinolone versus combination regimens without quinolones; any combination of drugs versus any monotherapy; and combination treatment administered for 30 days or less versus six weeks or longer. Our two predefined primary outcomes were relapse; and “overall failure,” defined as either therapeutic failure or relapse. Secondary outcomes included therapeutic failure; development of complications of disease; all cause mortality; any discontinuation of treatment; and any adverse events. See bmj.com.

Search strategy and analysis

We searched for all relevant studies regardless of language, publication status, or year of publication. See bmj.com for search terms. We searched conference proceedings for unpublished trials, trial registries for ongoing and unpublished trials and scanned the references of all included and excluded trials. Two reviewers performed the search, applied inclusion criteria and independently extracted data from included trials. Differences were resolved by discussion with a third reviewer. We contacted authors for clarifications and missing outcome data.

We calculated relative risks for dichotomous data. We pooled trials comparing similar regimens. Numbers needed to treat (NNT) were calculated as 1/risk difference obtained from a meta-analysis of the trials. We assessed methodological quality, and conducted

sensitivity and funnel plot analyses for the main comparison between tetracycline-aminoglycoside and tetracycline-rifampicin. We used a χ^2 test of heterogeneity and the I^2 measure of inconsistency to assess heterogeneity in the results of the trials. All analyses are shown using the fixed effect model, unless significant heterogeneity ($P < 0.1$) was present, in which case we used a random effect model. See bmj.com for details.

RESULTS

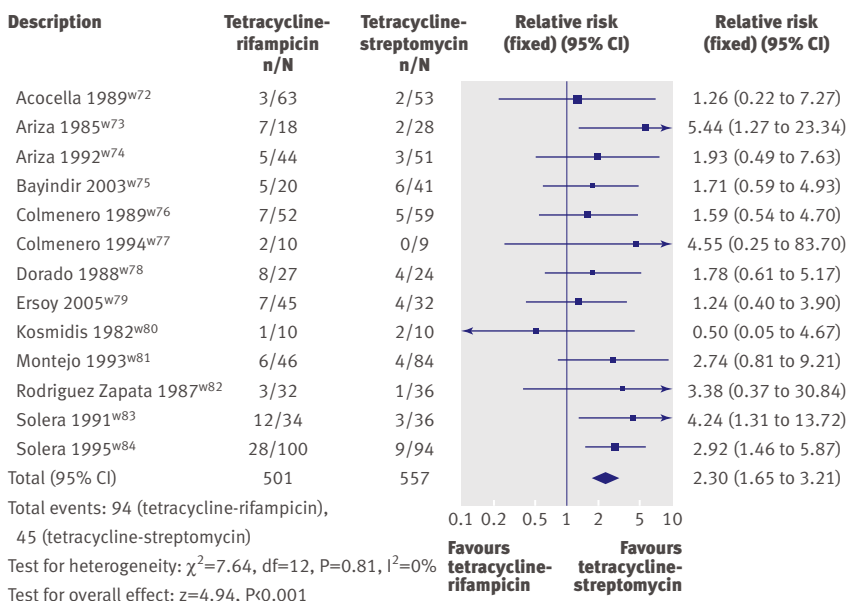
The search strategy resulted in 101 potentially relevant publications. After exclusions we included 30 randomised controlled trials comprising 77 treatment arms.^{w72-w100} Full characteristics of *Brucella* infection among included patients and exclusion criteria are in table A on bmj.com. No patients with *Brucella* endocarditis or neurobrucellosis were included. Follow-up ranged from 3 to 36 months. None of the trials reported on mortality as an outcome, nor were specific adverse events reported, except for ototoxicity, and only a few reported on the development of *Brucella* complications. Six trials reported adequate allocation concealment and 12 reported adequate allocation generation (see bmj.com). Two trials were double blind,^{w74 w97} and the remaining were open label.

Tetracycline-streptomycin v tetracycline-rifampicin

Thirteen trials, with 1058 patients, were included in this comparison.^{w72-w84} Streptomycin was administered for 21 days in eight trial arms and 14-15 days in six, while tetracycline and rifampicin were administered for the duration of treatment, 30-45 days. Overall failure was significantly higher with tetracycline-rifampicin (relative risk 2.30, 95% confidence interval 1.65 to 3.21; figure). We found no significant heterogeneity for the overall comparison ($P=0.81$, $I^2=0\%$). The difference with regard to overall failure originated mainly from a difference in relapse rates (2.86, 1.84 to 4.43). Therapeutic failure was higher with tetracycline-rifampicin, but the difference was not significant and of smaller magnitude (1.54, 0.87 to 2.71; 10 trials). Treatment with tetracycline-rifampicin had to be discontinued more often than treatment with tetracycline-streptomycin (1.43, 1.03 to 2.00). Adverse events in general and discontinuation because of adverse events were similar for the two treatment groups (1.08, 0.84 to 1.39, and 1.20, 0.40 to 3.59, respectively; values >1 favour the streptomycin arm). Ototoxicity was reported only in the tetracycline-streptomycin group (six of 262 patients, five trials).

When we restricted the analysis to doxycycline-streptomycin versus doxycycline-rifampicin we found a similar trend: a significant disadvantage with doxycycline-rifampicin with regard to overall failure (2.27, 1.62 to 3.16), relapse (2.80, 1.81 to 4.36), and rates of discontinuation (1.41, 1.01 to 1.97), without heterogeneity.

Subgroup and sensitivity analyses—Overall failure was higher with tetracycline-rifampicin among patients



Overall failure (defined as failure of assigned regimen or relapse) with tetracycline-rifampicin v tetracycline-streptomycin

with brucellosis confirmed by culture (2.79, 1.53 to 5.08; three trials) and among patients with complications of brucellosis (2.63, 1.41 to 4.93; four trials). Confidence intervals overlapped for all categories of methodological quality, although quasi-randomised trials tended to exaggerate the advantage of tetracycline-streptomycin. Exclusion of trials with inadequate concealment of allocation yielded a relative risk of 1.74 (1.14 to 2.65) for overall failure and 2.25 (1.27 to 3.98) for relapse. The funnel plots for overall failure and relapse did not show selection bias.

Quinolone v non-quinolone based regimens

Five trials compared quinolone-rifampicin with doxycycline-rifampicin.^{w75 w79 w93 w94 w98} Overall failure was non-significantly higher in the quinolone group (1.40, 0.77 to 2.52), with no heterogeneity ($P=0.63$, $I^2=0\%$). Both relapse (1.28, 0.64 to 2.53) and therapeutic failure (1.74, 0.59 to 5.19) were more common in the quinolone arm, but not significantly so. The analysis of adverse events favoured quinolone-rifampicin (0.37, 0.22 to 0.63; three trials). Discontinuation because of adverse events was reported in a single trial, with no significant difference.^{w79}

Two trials compared quinolone-rifampicin with doxycycline-streptomycin.^{w75 w79} Overall failure was higher in the quinolone arm (2.28, 1.17 to 4.46), with some heterogeneity ($P=0.13$, $I^2=57\%$). Relapse (3.21, 1.14 to 9.00) and therapeutic failure (1.57, 0.59 to 4.16) occurred more often with quinolones. There was no difference in rates of adverse events or discontinuation because of adverse events.

Comparison of any quinolone based regimen versus a regimen without a quinolone showed a significant disadvantage to the quinolone arm with regard to overall failure (1.83, 1.11 to 3.02), with some heterogeneity ($P=0.14$, $I^2=42.9\%$). Subgroup analyses were scarce. Overall failure was significantly higher with quinolone based regimens among patients with complicated brucellosis in two trials, without heterogeneity (2.93, 1.48 to 5.78).

Monotherapy v combination treatment regimens

Seven trials assessed monotherapy.^{w78 w81 w88-w92} When co-trimoxazole was the monotherapy, overall failure was not significantly different (1.27, 0.81 to 1.99; three trials, 257 patients), though therapeutic failure was more common (2.49, 1.26 to 4.89; three trials, 294 patients). For tetracycline monotherapy (two trials, 211 patients), the respective relative risks were 1.01 (0.58 to 1.77) and 0.25 (0.03 to 2.32). Two small trials that assessed ceftriaxone and ciprofloxacin as monotherapy were stopped early because of a significant disadvantage in the monotherapy arm.^{w91 w92} Two trials assessed six months of co-trimoxazole monotherapy compared with short term combination therapy (28 days).^{w81 w89} When we limited the analysis to trials that compared similar durations of treatment for combination treatment and monotherapy, overall failure was more common with monotherapy (2.56, 1.55 to 4.23; five trials), while the two trials that compared long monotherapy with short combination therapy found no significant difference.

Short (<30 days) v long (≥6 weeks) duration of treatment

Four trials compared duration of treatment with the same or similar regimens in both trial arms.^{w72 w80 w95 w97}

Overall failure was significantly more common with short treatment duration (3.08, 1.01 to 9.38; random effects model $P=0.07$ and $I^2=61.9\%$ for heterogeneity). Both therapeutic failure (3.02, 1.03 to 8.80) and relapse (1.70, 1.19 to 2.44) were significantly more common with the shorter duration, without significant heterogeneity.

Four trials examined short duration (21-30 days) doxycycline-streptomycin compared with long duration doxycycline-rifampicin.^{w72 w76 w80 w82} Relapse rates were non-significantly higher with short duration doxycycline-streptomycin (2.29, 0.87 to 6.03) with no significant heterogeneity. The differences in overall failure and therapeutic failure were not significant, and

Recommendations for the treatment of uncomplicated brucellosis among non-pregnant adults

	WHO/FAO 1986 ^a	Ioannina 2007 ^b	Current review*
First line regimen	Doxycycline 6 weeks + rifampicin 6 weeks	Doxycycline 6 weeks+streptomycin 2-3 weeks	Doxycycline 6 weeks+rifampicin 6 weeks +gentamicin 2 weeks OR doxycycline 6 weeks +gentamicin 2 weeks
Alternative	Tetracycline 6 weeks + streptomycin 2-3 weeks	Doxycycline 6 weeks+rifampicin 6 weeks	Doxycycline 6 weeks+streptomycin 2 weeks
Second line regimen		Doxycycline 6 weeks+gentamicin 1 week	Doxycycline+rifampicin 6 weeks OR tetracycline 6 weeks+gentamicin/streptomycin 2 weeks
Optional, poor evidence	Co-trimoxazole	Co-trimoxazole+doxycycline+other 6 weeks OR ofloxacin or ciprofloxacin+doxycycline+/-other 6 weeks	Co-trimoxazole+doxycycline/rifampicin 6 weeks
Not recommended		Azithromycin OR meropenem	Monotherapy OR <30 days of treatment OR quinolone with or without rifampicin/doxycycline

*Examines only drugs and regimens tested in randomised controlled trials. Duration of treatment (in table) and dosing recommendations based on durations and doses most commonly used in all included trials: doxycycline 100 mg twice daily; gentamicin 240 mg once daily; rifampicin 900 mg once daily; streptomycin 1g once daily; tetracycline hydrochloride 500 mg four times a day. Aminoglycosides administered intramuscularly and other drugs orally.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Several classic combination regimens are available for the treatment of brucellosis in addition to newer antibiotics, such as quinolones

Many randomised controlled trials have assessed these regimens, though the evidence has not recently been summarised

Treatment recommendations from authoritative sources are contradictory

WHAT THIS STUDY ADDS

A triple drug regimen of doxycycline, gentamicin, and rifampicin offers an advantage over doxycycline with an aminoglycoside, and doxycycline-aminoglycoside regimens are superior to doxycycline-rifampicin

Quinolones are inferior to other drugs

Six weeks' treatment is associated with a lower rate of relapse than shorter regimens

both comparisons were significantly heterogeneous (1.74, 0.35 to 8.72, and 4.02, 0.35 to 46.42, respectively, random effects model).

Other comparisons

Streptomycin v gentamicin—Two trials compared streptomycin with gentamicin, both in combination with a tetracycline.^{w85 w86} Rates of failure and relapse were higher with streptomycin, but the results were not significant (1.45, 0.52 to 4.00, for overall failure; 2.50, 0.56 to 11, for therapeutic failure; 1.19, 0.33 to 4.35, for relapse). Adverse events were similar overall, while adverse events leading to discontinuation were less common with gentamicin (0.19, 0.01 to 3.99). No heterogeneity was observed in these comparisons.

Dual v triple drug regimens—Two trials compared doxycycline-streptomycin with doxycycline-rifampicin-aminoglycoside.^{w75 w87} Overall failure was significantly higher with the dual drug regimen (2.50, 1.26 to 5.00, without heterogeneity). Rates of therapeutic failure (3.85, 1.37 to 11.0) and relapse (1.49, 0.55 to 4.0) were also in higher with the dual regimen, although the confidence intervals are wide. No adverse events that required discontinuation of treatment occurred in both trials.

Doxycycline v tetracycline—Four trials compared doxycycline with tetracycline. There were no differences between these drugs when administered for a similar duration of time (two trials).^{w75 w90} A shorter regimen of doxycycline-streptomycin was significantly inferior to a longer regimen of tetracycline-streptomycin (two trials, 6.25, 2.44 to 16.7, for overall failure).^{w72 w80}

Other—Two trials were not included in previous comparisons. One assessed the combination of cotrimoxazole-rifampicin compared with co-trimoxazole-doxycycline.^{w100} Overall failure and treatment failure were significantly more common without doxycycline (1.79, 1.08 to 2.98, and 2.86, 1.25 to 6.54, respectively). One small trial compared six with eight weeks of cotrimoxazole-rifampicin.^{w96} Overall failure was non-significantly higher with the shorter treatment (5.56, 0.70 to 44.09).

DISCUSSION

In this systematic review on the treatment of brucellosis we compared the specific drugs used in treatment regimens, monotherapy, dual and triple drug regimens, and duration of treatment in 30 randomised controlled trials.

The combination of tetracycline-streptomycin was significantly superior to tetracycline-rifampicin, mainly with regard to rates of relapse, with a number needed to treat of 11 (8 to 17) with tetracycline-streptomycin to prevent one relapse after treatment with tetracycline-rifampicin. The tetracycline administered to 1038 out of 1058 patients included in this comparison was doxycycline. Gentamicin could replace streptomycin in combination regimens for brucellosis. Quinolones were assessed in combination with rifampicin and were less effective than doxycycline with rifampicin or streptomycin.

Trials assessing monotherapy were less effective than combination therapy. Two trials assessed triple combination therapy with tetracycline-aminoglycoside-rifampicin and found it to be significantly more effective than the most effective dual regimen of tetracycline-aminoglycoside. The main difference was in primary failure of the regimen with an NNT of 10 patients (6 to 33) with triple combination therapy to prevent one therapeutic failure with dual therapy. Finally, treatment duration of six weeks or more resulted in a lower frequency of relapse than three to four weeks' treatment. Both long duration tetracycline-aminoglycoside and tetracycline-rifampicin were more effective than short duration tetracycline-aminoglycoside therapy, with NNTs of 20 (12 to 50) and 9 (5 to 100) patients, respectively, to prevent one relapse.

The table summarises the recommendations from our systematic review compared with previous recommendations.

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