Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials
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CRD summary
This review examined the efficacy of different antibiotic treatment regimens for brucellosis. The authors recommend long-term treatment using dual or triple regimens with an aminoglycoside. Given several limitations of the included studies, such as methodological differences and the poor quality of the included studies, and the pooling of clinically variable data, the authors' conclusions should be treated with caution.

Authors' objectives
To examine the effectiveness of different antibiotic treatment regimens in treating brucellosis.

Searching
PubMed and LILACS (from inception to June 2007), and the Cochrane CENTRAL Register (Issue 3, 2007) were searched without language restrictions; the search terms were reported. Conference proceedings and trial registries were also searched to identify ongoing or unpublished trials, and the references of relevant studies were screened.

Study selection
Randomised or quasi-randomised studies comparing single or combined antibiotic treatment with placebo, no treatment, or a different antibiotic regimen in adults or children with complicated or uncomplicated infections caused by Brucella spp., and reporting relapse and overall failure as the primary outcome, were eligible for inclusion. The included studies were conducted in European and middle Eastern countries and used mainly male patients without endocarditis or neurobrucellosis. A variety of treatment regimens were evaluated, and results for a number of secondary outcomes were also reported. The duration of follow-up ranged from 3 to 36 months.

Two reviewers screened studies for relevance, but it is unclear how any discrepancies were resolved.

Assessment of study quality
Validity was assessed on the basis of generation of allocation sequence, concealment of allocation, blinding and analysis. The authors did not state how many reviewers assessed validity, or how any discrepancies were resolved.

Data extraction
The outcomes were extracted on an intention-to-treat basis where possible. Relative risks (RRs) were calculated for dichotomous data, along with 95% confidence intervals (CIs).

Two independent reviewers extracted the data, and any discrepancies were resolved through discussion with a third reviewer.

Methods of synthesis
The RRs were pooled by treatment regimen using a fixed-effect model, unless significant heterogeneity was evident in which case a random-effects model was used. Heterogeneity was assessed using the $\chi^2$ and $I^2$ tests. Sensitivity analyses were conducted to investigate the severity of disease, drug regimens and study quality. A funnel plot analysis was conducted on studies comparing tetracycline-aminoglycoside and tetracycline-rifampicin, to determine the potential for selection bias.

Results of the review
Thirty randomised controlled trials (RCTs; n=3,975; 77 treatment arms) were included in the review. Sample sizes ranged from 11 to 1,100 patients.
Twelve studies reported adequate allocation generation, six reported adequate allocation concealment and only two were double-blind, with the remainder being open-label.

Tetracycline-streptomycin versus tetracycline-rifampicin (13 studies): overall failure was significantly higher in patients receiving tetracycline-rifampicin (RR 2.30, 95% CI: 1.65, 3.21, p<0.001), with the main difference originating from differences in relapse rates (RR 2.86, 95% CI: 1.84, 4.43, p<0.001), which translates into a number-needed-to-treat of 11 (95% CI: 8 to 17) with tetracycline-streptomycin to prevent one relapse after treatment with tetracycline-rifampicin. There were no significant differences between groups for therapeutic failure.

Quinolone versus non-quinolone-based regimen (5 studies): overall failure was significantly higher in patients receiving any quinolone regimen compared with those without quinolone (RR 1.83, 95% CI: 1.11, 3.02, p<0.02). Two studies comparing quinolone-rifampicin with doxycycline-streptomycin reported greater overall failure in the quinolone group (RR 2.28, 95% CI: 1.17, 4.46). However, heterogeneity was reported.

Monotherapy versus combination treatment (7 studies): significant heterogeneity was evident among studies comparing monotherapy with combination treatment regimens, thus meta-analysis could not be performed. Separate analyses by type of monotherapy showed mixed results.

Short- versus long-term treatment (6 studies): 4 studies reported significantly higher overall failure, therapeutic failure and relapse with shorter treatment durations; the RRs were 3.08 (95% CI: 1.01, 9.38, p=0.07), 3.02 (95% CI: 1.03, 8.80) and 1.70 (95% CI: 1.19, 2.44), respectively. There were no significant differences in primary outcomes when using short duration doxycycline-streptomycin compared with long duration doxycycline-rifampicin (4 studies).

Several analyses showed significant heterogeneity. Two studies reported significantly higher overall failure in short duration doxycycline-streptomycin compared with long duration tetracycline-streptomycin (RR 6.25, 95% CI: 2.44, 16.7).

The results for secondary outcomes were also reported in the review. For other comparisons (10 studies) where the number of trials were limited or the results non significant, secondary outcomes and sensitivity analyses were also reported.

Selection bias was not evident from the funnel plot analysis for overall failure and relapse, but no data were presented.

Authors' conclusions
Current treatment regimens for brucellosis differ significantly in their effectiveness. Treatment should preferably include dual or triple regimens and aminoglycosides, with the optimal treatment being doxycycline-aminoglycoside-rifampicin. Mono- or combination therapy with quinolones cannot currently be recommended.

CRD commentary
The review question was clear and was supported by appropriate inclusion criteria for the participants, interventions, outcomes and study design. A comprehensive literature search was performed using several appropriate sources and unpublished publications were sought. The authors acknowledged that they might have missed some non-English language studies. Validity was assessed, but the majority of the included studies were of a poor quality. Attempts were made to minimise reviewer error and bias during the study selection and data extraction processes, but it was unclear how many reviewers performed the validity assessment. Although appropriate methods were used to assess heterogeneity, clinical and methodological differences between the studies mean that pooling of the results may not have been appropriate. In addition, the CIs were wide. Given these considerations, and that only 2 studies compared dual versus triple drug treatment, the authors’ conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that the findings cannot be applied to patients with endocarditis or neurobrucellosis.

Research: The authors stated that further research is required to assess the safety and efficacy of triple drug regimens, while further comparisons of doxycycline-aminoglycoside and doxycycline-rifampicin are no longer needed. Further assessment of quinolones would be beneficial in triple drug regimens, possibly in combination with aminoglycosides, once more potent quinolones have been developed. Further assessment of patients with specific complications of
brucellosis, using prospective long-term observational studies, is also needed.

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