Intermittent or daily short course chemotherapy for tuberculosis in children: meta-analysis of randomized controlled trials

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CRD summary
This review concluded that twice weekly intermittent short course therapy was less likely to cure tuberculosis in children compared with daily therapy. This conclusion should be interpreted with some caution, as it is based on the per-protocol rather than the intention-to-treat analysis, and the included trials were small and of generally poor quality.

Authors’ objectives
To compare the effectiveness of intermittent and daily rifampicin containing chemotherapy in childhood tuberculosis.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews and MEDLINE were searched to December 2008 without language restriction. Search terms were reported. Reference lists of studies were handsearched.

Study selection
Randomised controlled trials that compared intermittent and daily rifampicin containing treatment regimens for children (aged 16 years or below) with pulmonary/extrapulmonary tuberculosis were eligible for inclusion. Eligible trials could be conducted in hospital or ambulatory settings and had to report on cure or significant improvement. Significant improvement was defined as symptomatic relief and/or radiologic clearing at the completion of the treatment course.

Included trials were conducted in Turkey, India and South Africa. The majority (94%) of children in the included trials had pulmonary tuberculosis; their mean age ranged from two to seven years, where reported. Intensive treatments included streptomycin or pyrazinamide combined with isoniazid and rifampicin, or isoniazid and rifampicin alone, for between two weeks and two months. In the intermittent treatment arms, intensive treatment was administered twice weekly, three times per week, and daily. Continuation therapy consisted of isoniazid and rifampicin for between four and 8.5 months; in some trials, this was only administered to the intermittent treatment group, with patients in the daily group continuing with the same treatment. All trials administered continuation treatment twice weekly in the intermittent therapy group and one trial also administered continuation treatment twice weekly in the daily group (this trial administered intensive treatment daily).

Two reviewers independently assessed trials for inclusion.

Assessment of study quality
Two reviewers independently assessed trials for methodological quality using the Jadad scale, which assessed trials according to randomisation, double-blinding and withdrawals/drop-outs, and assigned trial a score out of 5 points.

Data extraction
Two reviewers independently extracted dichotomous data to estimate odds ratios (OR) together with 95% confidence intervals (CIs). Data were extracted on an intention-to-treat and per-protocol basis.

Methods of synthesis
Summary odds ratios, together with 95% confidence intervals, were estimated using random-effects models. Heterogeneity was assessed using the $I^2$ test. Sensitivity analysis was performed by excluding trials one at a time from the meta-analysis.

Results of the review
Four RCTs were included (n=466 children, range 36 to 213). Trial quality was generally poor, with three trials scoring 2
and one scoring 3 on the Jadad scale.

Intermittent therapy was associated with lower cure rates (OR 0.27, 95% CI 0.14, 0.51) based on the per-protocol analysis, but no significant difference based on the intention-to-treat analysis. There was no evidence of heterogeneity ($I^2=0\%$).

When individual trials were excluded, none of the summary estimates based on the remaining three trials showed significant differences between treatment groups. There were no significant differences between treatment groups for adherence, relapse or drug-related side effects, but event rates were very low. One trial reported data for interrupted treatment and found no significant differences between groups.

**Authors’ conclusions**
Twice weekly intermittent short course therapy was less likely to cure tuberculosis in children as compared to daily therapy.

**CRD commentary**
The review addressed a focused question supported by clearly defined inclusion criteria. The literature search was adequate, but specific attempts were not made to locate unpublished studies, so there was a possibility of publication bias; steps were taken to minimise language bias. Appropriate steps were taken to minimise bias and errors at all stages of the review process.

Trial quality was assessed using some relevant criteria, but concealment of treatment allocation was not considered; the results of the analysis were simply presented as summary quality scores, with no details of the individual items fulfilled making the results difficult to interpret. Appropriate methods were used to pool trials; the results were clearly presented in tables and using forest plots, although the appropriateness of pooling was questionable given the differences in treatment regimes between trials.

The authors’ conclusion should be interpreted with some caution, as it is based on the per-protocol analysis rather than the intention-to-treat analysis and the included trials were small and of generally poor quality.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that there is a need for better quality RCTs to assess the efficacy of alternate schedules, including three times weekly therapy, for intermittent therapy for childhood tuberculosis.

**Funding**
None.

**Bibliographic details**

**PubMedID**
19578224

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by NLM
MeSH
Antibiotics, Antitubercular /administration & dosage; Child; Drug Administration Schedule; Humans; Randomized Controlled Trials as Topic; Rifampin /therapeutic use; Treatment Outcome; Tuberculosis /drug therapy

AccessionNumber
12010001572

Date bibliographic record published
16/06/2010

Date abstract record published
06/10/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.