Effectiveness of standard short-course chemotherapy for treating tuberculosis and the impact of drug resistance on its outcome

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CRD summary
This well-conducted review assessed standard short-course chemotherapy for patients with tuberculosis. The author concluded that the target cure rate of 85% is not achievable using an intermittent regimen, and that the World Health Organization directly observed treatment short-course-plus multi-drug resistant programme should be adopted. These conclusions are not supported by the results of the review, as they were not directly assessed.

Authors' objectives
To assess the effectiveness of standard short-course chemotherapy (SCC) for the treatment of patients (new patients and re-treatment of patients) with pulmonary tuberculosis (TB), and to assess the impact of drug resistance on the outcome of standard SCC.

Searching
MEDLINE, EMBASE, Current Contents, CINAHL, Expanded Academic ASAP, PsycINFO, AUSThealth, DARE and the Cochrane Library were searched from 1993 to 2002. The reference lists of identified studies were checked for additional studies. The author also searched Dissertation Abstracts International and Index to Theses in an attempt to identify unpublished studies. The websites of the WHO and the International Union against Tuberculosis and Lung Disease were also searched. The author did not state whether any language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-RCTs were eligible for inclusion. The author stated that studies using other research methods were assessed for inclusion in the review as a narrative summary. All of the included studies were cohort studies.

Specific interventions included in the review
For new cases, SCC regimens consisting of four drugs during the initial phase (2 months) followed by two drugs during the continuation phase (4 months) were eligible for inclusion. For re-treatment cases, SCC regimens consisting of five drugs during the initial phase followed by three drugs during the continuation phase, with a total treatment duration of 8 months, were eligible for inclusion. Both daily and intermittent regimens were eligible for inclusion. Some of the included studies used World Health Organization (WHO) recommended treatment regimens. A three-drug treatment combination regimen was used during the initial phase in some studies and during the continuation phase only in one study. Some studies used the intermittent regimen. Some studies assessed directly observed therapy.

Participants included in the review
Patients with pulmonary TB, including new patients and re-treatment patients, aged at least 16 years with positive growth on culture of Mycobacterium tuberculosis and susceptibility test results were eligible for inclusion. Most of the studies included civilian TB patients; however, one study included prisoners and one study included gold miners infected with the human immunodeficiency virus. The majority of the included studies were conducted in Asia, while the others were conducted in Europe, North America and South Africa; one study was conducted in six different countries.

Outcomes assessed in the review
The outcomes of interest were results of susceptibility testing for first-line anti-TB drugs and six standardised treatment outcomes of the WHO:
cure (defined as a patient who is smear negative at, or one month prior to, completion of treatment and on at least one
previous occasion);
treatment completed (defined as a patient who has completed treatment but without proof of cure);
treatment success (obtained by adding the percentage of cure cases and the percentage of cases in whom treatment was completed);
treatment failure (defined as a patient who remains or becomes smear-positive again at 5 months or later during treatment);
died (defined as a patient who dies for any reason during the course of therapy);
treatment interrupted or default (defined as a patient whose treatment was interrupted for at least 2 months);
transfer out (defined as a patient who has been transferred to another reporting unit and for whom the treatment outcome is not known).

Most of the included studies assessed outcomes at the end of the treatment period.

**How were decisions on the relevance of primary studies made?**
Two reviewers independently assessed studies for inclusion in the review, and any disagreements were resolved through discussion with a third reviewer.

**Assessment of study quality**
The methodological quality of the included studies was assessed using a checklist developed by the Joanna Briggs Institute, which assessed the following criteria: study based on a random or pseudo-random sample; clearly defined inclusion criteria; outcome assessment using objective criteria; sufficient description of groups (comparison studies only); appropriate statistical analysis. Only studies that scored 4 or more points, out of a possible 5, were included in the review.

The checklist was pilot tested prior to use. Two reviewers independently assessed the quality of the included studies, and any disagreements were resolved through discussion with a third reviewer.

**Data extraction**
Two reviewers independently extracted data from the included studies onto a data extraction form that was developed for the review. Any disagreements were resolved through discussion with a third reviewer. When necessary, the principal authors of included studies were contacted for additional data or clarification.

Treatment success was calculated by adding together the proportion of cure cases and the proportion of cases that completed treatment.

**Methods of synthesis**
*How were the studies combined?*
The studies were combined in a narrative.

*How were differences between studies investigated?*
Differences between the studies were discussed.

**Results of the review**
The literature searches identified 20 studies that met the review inclusion criteria. Eleven cohort studies (n=14,382) scored 4 or more on the quality assessment and so were included in the review.
Effectiveness of standard SCC for treating TB.

The success rate of 6-month daily regimens for new TB patients was between 84 and 86% (2 studies); however, the cure rate was only 58% in Italy, compared with 82 to 86% in Korea, Hong Kong and Africa.

The success rate for intermittent regimens was between 59 and 89% (3 studies); however, the cure rates were only 26%, 35% and 43% in the Dominican Republic, Ivanovo Oblast and China, respectively.

The 3-drug combination had a success rate and cure rate of between 81 and 84% (2 studies).

For patients being re-treated for TB, daily regimens had a success rate of between 50 and 72% (2 studies); the highest cure rate was 68% in Turkey and the lowest was 50% in Korea. Intermittent regimens had a success rate of between 22 and 69% (3 studies); however, the cure rate was only 8% in the Dominican Republic, compared with 39 to 64% in China, Ivanovo Oblast and Peru.

Effectiveness of SCC according to Mycobacterium tuberculosis drug susceptibility.

For new TB patients, the success rate of a daily regimen of SCC for drug-sensitive TB was on average 87% (1 study). The success rate of intermittent regimens for drug-sensitive TB was on average 72% (2 studies), while the 3-drug combination had a success rate of 85%. Drug resistance had a negative impact on the outcome of SCC: the success rates for the daily regimen, intermittent regimens and the 3-drug combination were reduced to 79%, 62% and 75%, respectively. Multiple-drug resistance had a large negative impact on the outcome of SCC, reducing the success rates even further to 52% for the daily regimen and 43% for intermittent regimens; data were not available for the 3-drug regimen.

For patients being re-treated for TB, the success rate of a daily regimen of SCC for drug-sensitive TB was on average 71% (1 study). The success rate of intermittent regimens for drug-sensitive TB was on average 54% (2 studies). Again, drug resistance had a negative impact on the outcome of SCC: the success rates for the daily regimen and the intermittent regimens were reduced to 46% and 32%, respectively. Multiple-drug resistance had a large negative impact on the outcome of SCC, reducing the success rates even further to 19% for the daily regimen and 22% for the intermittent regimens.

Authors' conclusions

There is insufficient evidence to draw conclusions regarding the effectiveness of SCC. The WHO-targeted cure rate of 85% in new smear-positive TB cases is not achievable using intermittent regimen SCC, and the target rate should be adjusted. The WHO directly observed treatment short-course-plus multi-drug resistant TB programme should be adopted. However, the evidence is limited to cohort studies.

CRD commentary

The review question was clear in terms of the interventions, participants, study designs and outcomes of interest. A number of relevant electronic databases and websites were searched and attempts were made to identify unpublished data. It was unclear whether any language restrictions were applied. The quality of the included studies was assessed using appropriate criteria, and only studies achieving a quality score of 4 out of a possible 5 were included in the review. The study selection, data extraction and quality assessment processes were carried out in duplicate, which helps to reduce errors and reviewer bias.

Adequate details of the included studies were provided in an appendix. The narrative synthesis was appropriate. The author concluded that the WHO-targeted cure rate of 85% is not achievable using intermittent regimen SCC. However, the evidence presented shows that this has not been achieved in the studies reviewed, but it is not possible to comment on whether this is achievable. The author appropriately cautioned that the evidence is limited in this area. The author's conclusion, that the WHO directly observed treatment short-course-plus multi-drug resistant TB programme should be adopted, cannot be verified as this programme was not assessed by the included studies.
Implications of the review for practice and research
Practice: The author stated that the evidence shows that treatment with daily regimens is effective for new TB cases, with a success rate of over 80%. To obtain a success rate of over 80% when an intermittent regimen is administered, a 100% directly observed treatment strategy is necessary. The WHO-targeted cure rate of 85% is not achievable using an intermittent regimen. In developing countries the use of WHO regimens under directly observed treatment strategies is clearly effective and is the best evidence-based practice.

Research: The author stated that the evidence is limited by the lack of good-quality research, particularly in terms of drug sensitivity and resistance. Good-quality research on the effectiveness of standard SCC for multiple-drug resistant TB is urgently required, particularly in view of the larger numbers of people infected with TB every year.

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