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Tuberculosis

QUESTIONS: What are the effects of different treatment regimens in people with newly diagnosed pulmonary tuberculosis? What are the effects of different drug regimens in people with multidrug-resistant tuberculosis? Which interventions improve adherence to treatment?

INTERVENTIONS

Beneficial

World Health Organization (WHO) short-course treatment (see glossary)
Antituberculous prophylaxis in people with HIV infection

Likely to be beneficial

Intermittent short-course treatment
Staff training, prompting mechanisms, enablers/cash incentives, health education, and directly observed treatment

Unknown effectiveness

Regimens containing quinolones
Comparative benefits of different regimens in multidrug-resistant tuberculosis
Sanctions for nonadherence to treatment

Likely to be ineffective or harmful

Treatment for less than 6 months

DEFINITION

Tuberculosis is caused by *Mycobacterium tuberculosis* and can affect many organs. Specific symptoms relate to the site of infection and are generally accompanied by fever, sweats, and weight loss.

INCIDENCE/PREVALENCE

About one third of the world's population is infected with *M tuberculosis*. The organism kills more people than any other infectious agent. The World Health Organization estimates that 95% of cases occur in developing countries and that 25% of avoidable deaths in those regions are caused by tuberculosis.[1]

ETIOLOGY

Social factors that increase risks include poverty, overcrowding, homelessness, and inadequate health services; medical factors include infection with HIV and immunosuppression.

PROGNOSIS

The prognosis varies widely and depends on treatment.[2]

AIMS

To cure tuberculosis, eliminate the risk of relapse, reduce infectivity, avoid emergence of drug resistance, and prevent death.

OUTCOMES

M tuberculosis in sputum (smear examination and culture); symptoms; weight; rates of relapse.

METHODS

We searched MEDLINE from 1966 to 1998 (key words: tuberculosis, pulmonary; trial, randomized controlled trial, controlled trial; isoniazid, pyrazinamide, rifampicin). We included all Cochrane systematic reviews, studies that were randomized or used alternate allocation, studies that had over 300 patients, and studies that had at least 1-year follow-up after completion of treatment.

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Summary Points

- Randomized controlled trials (RCTs) have found no differences in relapse rates between standard WHO short-course chemotherapy (6 months) and longer-term chemotherapy (8 to 9 months) in people with pulmonary tuberculosis. Use of pyrazinamide in the first 2 months seems to speed up sputum clearance but makes no difference in relapse rates. Extending its use beyond the first 2 months confers no additional benefit.
- We found limited evidence suggesting that there is no difference between daily and thrice-weekly short-course regimens. Reducing the duration of treatment from 6 to 4 months results in higher relapse rates.
- We found no good evidence comparing regimens containing quinolones with existing regimens.
- We found no good evidence comparing different drug regimens for multidrug-resistant tuberculosis.
- We found limited evidence suggesting that adherence to treatment may be improved by staff training, prompting mechanisms, enablers and cash incentives, health education, and direct patient observation. Sanctions for nonadherence to treatment have not been adequately evaluated.
- We found one RCT comparing the effect of directly observing patients while they take their treatment with allowing self-treatment at home. Nonrandomized tuberculosis strengthening programs, which include direct observation, have found improved adherence.

Glossary
WHO short-course chemotherapy includes 6 months of treatment, with 4 drugs in the first 2 months (isoniazid, rifampicin, pyrazinamide, and either ethambutol or intramuscular streptomycin), and 2 drugs in the subsequent 4 months (rifampicin and isoniazid).

QUESTION: What are the effects of different drug regimens in people with newly diagnosed pulmonary tuberculosis?

OPTION: SHORT-COURSE CHEMOTHERAPY

RCTs found no difference in relapse rates between WHO short-course chemotherapy (6 months—see glossary) and longer-term (8- to 9-month) chemotherapy in people with pulmonary tuberculosis. Use of pyrazinamide in the first 2 months was found to speed up sputum clearance but made no difference to relapse rates. Extending the use of pyrazinamide beyond the first 2 months conferred no additional benefit.

Benefits

We found no systematic review. Two RCTs published in the mid-1980s compared 6 versus 8 or 9 months' chemotherapy in a total of 1295 people with untreated culture- or smear-positive pulmonary tuberculosis.[3,4] Participants were followed up for at least 1 year after treatment was completed. The trials, performed in the United Kingdom and in east and central Africa, used different combinations of isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide for initial (first 2 months) and continuation treatment. Overall, there was no significant difference between short-course and longer regimens. Extending the use of pyrazinamide beyond the first 2 months did not improve cure rates. Sputum conversion was faster with regimens containing pyrazinamide, but there was no difference in relapse rates at 3-year follow-up.[4] There was no difference between regimens using ethambutol or streptomycin as the fourth drug in the initial phase.[4] A 6-month regimen using rifampicin and isoniazid throughout was highly effective (relapse rate, 2%) and was significantly better than isoniazid used alone in the 4-month continuation phase (relapse rate, 9%). When use of isoniazid alone was prolonged in a 6-month continuation phase, the relapse rate was not significantly better than with 4-month continuation.[3]

Harms

In the largest trial, possible adverse reactions were reported in 24 of 851 patients (3%), with only 6 requiring modification of treatment.[3] Two patients in this study developed jaundice, 1 of whom died.

Pyrazinamide

Adding pyrazinamide did not increase the incidence of hepatitis (4% with and without pyrazinamide).[4] Mild adverse effects were more common, however, including arthralgia, skin rashes, flu-like symptoms, mild gastrointestinal disturbance, vestibular disturbance, peripheral neuropathy, and confusion. Arthralgia was the most common adverse effect, reported in about 0.7% of patients on pyrazinamide,[3,4] but symptoms were mild and never required modification of treatment.

Comment

In patients who have been previously treated, the organisms may have acquired drug resistance, so WHO short-course chemotherapy may not be effective.

OPTION: INTERMITTENT DOSING

The limited data we found provide no evidence of a difference between daily and thrice-weekly short-course regimens but do not exclude a clinically significant difference.

Benefits

One systematic review published in January 1999 identified 1 RCT comparing 3 times per week versus daily chemotherapy for 6 months in 399 people with newly diagnosed pulmonary tuberculosis.[5] At 1 month after treatment was completed, there was no significant difference in rates of bacteriological cure, defined as negative sputum culture (99.9% vs 100%), or in relapse (5 patients vs 1 patient). At least 12 cohort studies have found cure rates of 80% to 100% with thrice-weekly regimens taken for 6 to 9 months.[5]

Harms

Intermittent treatment has the potential to contribute to drug resistance, but this was not shown in these studies.[5]

Comment

The number of people randomly allocated was too small to exclude a clinically significant difference between the dosing regimens.

OPTION: CHEMOTHERAPY FOR LESS THAN 6 MONTHS

We found limited evidence suggesting that reducing the duration of treatment to less than 6 months results in unacceptably high relapse rates.

Benefits

We found 1 systematic review that included 7 RCTs published between 1979 and 1989 on outpatients with newly diagnosed pulmonary tuberculosis.[6] The trials randomly allocated 228 and 2020 people in India, Hong Kong, Singapore, and Germany, comparing a variety of shorter (minimum 2 months) and longer (maximum 12 months) drug regimens. Relapse rates were consistently higher after the shorter duration treatments.

Harms
There was little difference in adverse events or toxicity except in 1 trial, which found that patients given a 2-month regimen were less likely to change or discontinue drugs than those given a 12-month regimen. Numbers, however, were small (6/299 vs 17/299).[6]

Comment
The treatments were given under ideal conditions. In clinical practice, relapse rates with shorter regimens are likely to be worse.

OPTION: REGIMENS CONTAINING QUINOLONES
Regimens containing quinolones have not been adequately compared with existing regimens in people with tuberculosis.

Benefits
We found no systematic review. One RCT of 200 patients from Tanzania found no significant difference in the rate of treatment failure between a regimen containing ciprofloxacin and a regimen not containing it (RR of relapse at 6 months 16, 95% confidence interval [CI] 0.94 to 278).[7] A relatively low dosage of ciprofloxacin was used (750 mg daily).

Harms
None reported

Comment
Quinolones have good bactericidal activity in vitro. Some of the newer quinolones have enhanced anti-mycobacterial activity compared with ciprofloxacin.

QUESTION: What are the effects of different drug regimens in people with multidrug-resistant tuberculosis?

Different drug regimens for multidrug-resistant tuberculosis have not been adequately compared.

Benefits
We found no systematic reviews and no RCTs comparing different regimens in people with multidrug-resistant tuberculosis.

Harms
Insufficient data

Comment
Current clinical practice in multidrug-resistant tuberculosis is to include at least 3 drugs to which the particular strain of tuberculosis is sensitive, using as many bactericidal agents as possible. Patients are directly observed and managed by a specialized clinician.

QUESTION: Which interventions improve adherence to treatment?

OPTION: STAFF TRAINING
We found limited evidence suggesting that training of health staff improves adherence.

Benefits
We found 1 systematic review, updated in November 1998,[8] which identified 1 RCT that compared intensive staff supervision with routine supervision at Korean centers performing tuberculosis extension activities. Centers were paired and randomized. Supervision was carried out by senior doctors. Higher completion rates were achieved with intensive supervision (RR 1.2, confidence intervals not yet available as cluster effect not yet corrected for).

Harms
None reported

Comment
The effect on adherence was modest, and we cannot yet say whether it was significant.

OPTION: PROMPTING MECHANISMS
RCTs have found that prompting mechanisms improve adherence.

Benefits
We found 1 systematic review that identified 2 RCTs.[8] The first compared reminder cards versus usual follow-up in people who did not collect their drugs after discharge from hospital. Those in the intervention group were more likely to complete their treatment (RR 1.2, 95% CI 1.1 to 1.4). The second trial, in the United States, compared the use of peer health advisers who met participants and went to the clinic with them. It found that there was increased attendance at the first follow-up appointment (RR versus no intervention 1.4, 95% CI 1.1 to 1.8).

Harms
None

Comment
Both were small studies from which it is not possible to generalize widely. Implementing prompting mechanisms in larger populations would require well-staffed and well-organized tuberculosis programs. It is not known whether the same effects would be observed in regional or national programs.

OPTION: ENABLERS
RCTs have found that cash incentives improve adherence among people living in deprived circumstances.

Benefits

We found 1 systematic review that identified 2 RCTs, both from the United States.[8] One, among homeless men, found that money ($5) improved attendance at the first appointment (RR 1.6, 95% CI 1.3 to 2.0). The other, among migrants, found that combining cash ($10) with health education improved attendance compared with usual care (RR 2.4, 95% CI 1.5 to 3.7).

Harms

None measured

Comment

None

OPTION: HEALTH EDUCATION

The effects of health education alone on adherence have been poorly evaluated in the limited evidence we found.

Benefits

We found 1 systematic review that identified 1 RCT, conducted in the United States,[8] comparing education by a doctor at a clinic versus giving the participant a leaflet. It found no significant difference in the proportion of participants completing treatment, although numbers were small.

Harms

None measured

Comment

The trial was probably too small to exclude an effect of health education. Other RCTs have evaluated health education as part of a motivational package, such as nurses phoning patients every 3 months. Its inclusion in a more complex package makes it difficult to evaluate the effects of education alone.

OPTIONS: SANCTIONS

Sanctions for failure to adhere to treatment have not been adequately evaluated in the evidence we found.

Benefits

We found 1 systematic review, but it identified no RCTs of sanctions.[8]

Harms

The use of sanctions may be ethically dubious because it reduces or removes a patient's choice.

Comment

In New York, the "locked hospital" was thought to have given credibility to the Department of Health's strategy for curing some patients.[9]

OPTION: DIRECT PATIENT OBSERVATION

One RCT has found that directly observing patients as they take their drugs makes little difference to adherence. Observational evidence, however, suggests that tuberculosis-strengthening programs, which usually include direct observation (often called directly observed therapy short-course programs or DOTs), can improve adherence.

Benefits

We found 1 systematic review that identified 1 RCT, conducted in South Africa, comparing direct observation of patients versus self-administered treatment at home.[8] It found no difference between the 2 strategies, although overall adherence in the study was low.

Harms

Potential harms include reduced cooperation between patient and doctor, removal of responsibility from patients, detrimental to long-term sustainability of anti-tuberculosis programs, and increased burden on health services to the detriment of care for other diseases. None of these has been adequately investigated.

Comment

Numerous observational studies have evaluated interventions described as DOTs, but all were intervention packages that included further anti-tuberculosis programs such as strengthening drug supplies, improving microscopy services, and offering numerous incentives, sanctions, and cointerventions likely to influence adherence.[10]

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