

TUBERCULOSIS

**EVIDENCE-BASED
INTERVENTIONS
FOR DIAGNOSING,
PREVENTING
AND TREATING
TUBERCULOSIS**

MAY 2014



Introduction

Tuberculosis occurs all over the world, particularly in poorer regions, and where human immunodeficiency virus (HIV) is common. Over 95% of tuberculosis deaths occur in developing countries and it is among the top three causes of death for women between the ages of 15-44.

This booklet provides summaries of Cochrane systematic reviews for the diagnosis, prevention and treatment of tuberculosis.

What is a Cochrane systematic review?

A Cochrane systematic review asks a specific research question about a particular healthcare intervention in a clearly defined group of people with a health condition or problem; for example *does isoniazid prevent Tuberculosis in non-infected HIV persons*. These reviews summarise the results of healthcare studies and provides the evidence on the effectiveness of the interventions. These reviews are produced by The Cochrane Collaboration and it is published in an online database, *The Cochrane Library* (www.thecochranelibrary.com)

The South African Cochrane Centre (SACC)

The SACC (www.mrc.ac.za/cochrane) based at the South African Medical Research Council in Cape Town is part of the international Cochrane Collaboration (www.cochrane.org), a non-profit organization. The vision of the SACC is that healthcare decision-making within Africa will be informed by high quality, timely and relevant research evidence.

The Cochrane Consumer Network (CCNet)

The CCNet consists of people committed to the importance of consumer participation in informed healthcare decision-making processes. The Network promotes the use of evidence-based healthcare to guide well-informed decisions about health care. CCNet offers communication support and training on using evidence to enable consumers to sift through the facts and benefit from The Cochrane Collaboration's systematic reviews on evidence-based healthcare. To learn more about CCNet visit their website <http://consumers.cochrane.org/healthcare-users-cochrane>

Diagnosis

Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Accurate and rapid detection of tuberculosis and drug resistance are critical for improving patient care and decreasing the spread of TB. Xpert® MTB/RIF assay (Xpert) is a rapid, automated test that can detect both TB and rifampicin resistance, within two hours after starting the test, with minimal hands-on technical time, but is more expensive than conventional sputum microscopy. This review assessed the diagnostic accuracy of Xpert for pulmonary TB (TB detection), both where Xpert was used as an initial test replacing microscopy, and where Xpert was used as an add-on test following a negative smear microscopy result. It also assessed the diagnostic accuracy of Xpert for rifampicin resistance detection where Xpert was used as the initial test, replacing conventional culture-based drug susceptibility testing. The assessment was made in the adult population suspected of having pulmonary TB or multidrug-resistant TB (MDR-TB), with or without HIV infection. Most studies were performed in high TB burden countries.

Summary: Tuberculosis (TB) causes tremendous suffering worldwide, especially in low-income and middle-income countries. In 2012, 8.6 million people developed TB disease (active TB) for the first time and around 1.3 million people died. Most people with TB can be cured if the disease is diagnosed and properly treated. One of the problems in treating TB is that the bacteria become resistant to antibiotics. Detecting TB and TB drug resistance quickly is important for improving health, reducing deaths, and decreasing the spread of TB in communities.

Xpert® MTB/RIF is a new test that quickly detects TB and rifampicin resistance at the same time. Rifampicin is an important drug for treating people with TB. Since the test is automated, it does not require expert staff or an advanced laboratory.

Our objectives were to determine the diagnostic accuracy ([sensitivity](#) and [specificity](#)) for TB detection and rifampicin resistance detection. Sensitivity shows how often the test gives a positive result in people who really have TB. Specificity shows how often the test gives a negative result in people who do not have TB.

We included studies of adults with or without HIV infection thought to have [pulmonary](#) TB (TB in the lungs) or rifampicin resistance, and were most interested in the use of Xpert® MTB/RIF outside of the most advanced laboratories.

We also compared the [sensitivity](#) of Xpert® MTB/RIF to that of smear microscopy, the test commonly used for TB diagnosis in low- and middle-income countries. Smear microscopy is low-cost and fairly easy to do, but requires trained staff and is a hassle for patients, who must provide at least two [sputum](#) samples. Also, microscopy gives no information about drug resistance.

We searched for publications in any language up to 7 February 2013 and considered the [study's risk](#) of giving biased results.

What the results say

We included 27 studies involving around 9500 people. Most studies were performed in low- or middle-income countries. We thought most studies had a low [risk](#) of [bias](#).

The key findings were:

For TB detection, Xpert® MTB/RIF was accurate (it was highly sensitive (89%), detecting almost all cases; and specific (99%), that is, not registering positive in people who were actually negative).

For rifampicin resistance detection, Xpert® MTB/RIF was accurate that is sensitive (95%) and specific (98%).

Xpert® MTB/RIF appeared to have similar accuracy in people with and without HIV infection.

Applying the findings of the [review](#) to an imaginary group of 1000 people who go to their doctor with symptoms, but where only 100 of them (10%) actually have TB, Xpert® MTB/RIF would diagnose 88 cases and miss 12 cases, whereas smear microscopy would diagnose 65 cases and miss 35 cases.

To summarize, our [review](#) shows that Xpert® MTB/RIF is more accurate than smear microscopy for diagnosing TB and also accurate for detecting rifampicin resistance. Xpert® MTB/RIF may be useful in many countries, as it does not require advanced laboratory facilities or expert staff.

Citation: Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD009593. DOI: 10.1002/14651858.CD009593.pub3

Prevention

Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children

Children with human immunodeficiency virus (HIV) are at an increased risk of acquiring tuberculosis. Even with treatment, HIV-infected children with tuberculosis have a worse outcome than children with tuberculosis only. This review evaluates the impact of tuberculosis preventive therapy on tuberculosis incidence and death in HIV-infected children.

Summary: Tuberculosis (TB) is a common cause of severe lung disease and death in children infected with HIV, particularly those living in areas of high tuberculosis prevalence. Hence preventing TB infection and disease in HIV-infected children is desirable and potentially an important major public health intervention. Isoniazid, a medication used in the treatment of TB, has been effectively used to prevent TB in HIV-uninfected children exposed to TB. However, it is unclear what impact TB preventive therapy such as isoniazid has on the rate of TB or death if given to HIV-infected children with and without exposure to TB. This review aimed to assess the impact of any TB preventive therapy on the rate of TB or death when given to HIV-infected children. We found only one published randomised controlled trial investigating TB preventive therapy in HIV-infected children. The trial showed a marked reduction in TB incidence and death in the group of children who received isoniazid as primary preventive therapy. Few adverse events occurred during the study and none were related to the isoniazid therapy. However there are currently no long-term follow up data on the durability of the protective effect or possible long term adverse events. This trial was also unable to assess the impact of isoniazid prophylaxis on children receiving antiretroviral therapy. Further studies are needed to assess whether TB preventive therapy is of benefit in all HIV-infected children irrespective of use of antiretroviral treatment; the optimal duration of preventive therapy or long term adverse effects.

Citation: Gray DM, Young T, Cotton M, Zar H. Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD006418. DOI: 10.1002/14651858.CD006418.pub2

Isoniazid for preventing tuberculosis in non-HIV infected persons

Although isoniazid is commonly used for treating tuberculosis, it is also effective as preventive therapy. This review estimates the effect of six- and 12-month courses of isoniazid for preventing tuberculosis in HIV-negative people at increased risk of developing active tuberculosis.

Summary: Tuberculosis (TB) is a serious bacterial infection and it is estimated that about a third of the world's population is infected with TB. There are a number of types, such as pulmonary TB (bacteria residing in a person's lungs) and spinal TB (in the spine). Some bacteria can be drug resistant and some people may have the infection alongside another medical condition. People suffer from severe cough, weakness and sweats, and some people still die from TB even though effective drug treatment has been around for many years. The incidence of TB has reduced in areas where the drugs are readily available. Preventing people from contracting TB in high-risk areas is a goal worth pursuing. The review of trials using isoniazid for a six- to 12-month period in people without HIV infection (HIV infected people were studied in another review) identified 11 trials involving over 90,000 people. Isoniazid was effective in preventing TB in 60% of people, although some did develop hepatitis. The findings showed that one person can be saved from getting TB when 35 people take isoniazid for six months, and one in every 200 treated will get hepatitis. The balance of benefits and harms need to be carefully considered for each setting where intervention is being considered.

Citation: Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database of Systematic Reviews 1999, Issue 1. Art. No.: CD001363. DOI: 10.1002/14651858.CD001363

Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis

The emergence and spread of multiple-drug-resistant tuberculosis (MDR-TB), caused by strains of Mycobacterium tuberculosis resistant to at least isoniazid and rifampicin, is a potential threat to global tuberculosis control. Treatment is prolonged, expensive, more toxic than treatment of susceptible tuberculosis, and often unsuccessful. Experts are still undecided on the management of people exposed to MDR-TB. This review evaluates antituberculous drugs given to people exposed to MDR-TB in preventing active tuberculosis.

Summary: The emergence and spread of MDR-TB, caused by strains of *Mycobacterium tuberculosis* resistant to at least the common drugs used for TB (isoniazid and rifampicin), is a threat to people worldwide. Treatment of latent tuberculosis (infection without active disease) has been a key component in tuberculosis control for several decades. However, MDR-TB is spreading and people are dying. This review of evidence found no randomized controlled trials that have assessed the effectiveness of treatments of latent tuberculosis infection in people exposed to MDR-TB. Currently the balance of benefits and harms associated with treatment for latent tuberculosis infection in people exposed to MDR-TB is far from clear. Drug treatments should only be offered within the context of a well-designed randomized controlled trial, or where people are given the details of the current evidence on benefits or harms, along with the uncertainties.

Citation: Fraser A, Paul M, Attamna A, Leibovici L. Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005435. DOI: 10.1002/14651858.CD005435.pub2

Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Preventing active tuberculosis (TB) from developing in people with latent tuberculosis infection (LTBI) is important for global TB control. Isoniazid (INH) for six to nine months has 60% to 90% protective efficacy, but the treatment period is long, liver toxicity is a problem, and completion rates outside trials are only around 50%. Rifampicin or rifamycin-combination treatments are shorter and may result in higher completion rates. This review compares the effects of rifampicin monotherapy or rifamycin-combination therapy versus INH monotherapy for preventing active TB in HIV-negative people at risk of developing active TB.

Summary: Tuberculosis (TB) is a disease that is caused by a bacterial infection that affects an estimated two billion people (about a third of the world's population). However, most people have dormant (latent) infections and only a small percentage of people infected with TB will develop an active disease. Preventing latent TB infection (LTBI) developing into active TB, through the use of drugs, is an important part of global TB control. Treatment with the drug isoniazid for six months is recommended, but the treatment period is long, it can cause liver damage, and only about half of the people who start this drug treatment complete it.

The authors of this review evaluated alternatives to isoniazid monotherapy in HIV-negative people with LTBI. They identified 10 randomized controlled trials that included 10,717 adults and children, who were mostly HIV-negative, with a follow-up period ranging from two to five years.

Rifampicin for three to four months may give quite similar results to isoniazid for six months in preventing TB, and may cause fewer side effects. As the treatment period with rifampicin is shorter, it may result in more people completing treatment. Two other drug combination treatments (rifampicin plus isoniazid, and rifampicin plus pyrazinamide) did not differ in preventing TB compared with isoniazid alone, but they resulted in more adverse events. A third combination of rifapentine plus isoniazid supervised weekly for three months was as effective in preventing TB as self-administered isoniazid for nine months, increased treatment completion, and caused less liver toxicity, though treatment-limiting adverse events were more frequent with the weekly rifapentine and isoniazid combination.

Citation: Sharma SK, Sharma A, Kadiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD007545. DOI: 10.1002/14651858.CD007545.pub2

Treatment with drugs

Intermittent versus daily therapy for treating tuberculosis in children

Childhood tuberculosis (TB) is a neglected global public health problem. Short treatment courses with rifampicin-containing anti-TB drugs given daily for six-months cure over 90% of infected children, but poor adherence reduces treatment success. Intermittent, short-course anti-TB regimens, given two or three times a week under direct observation, are associated with higher adherence in observational studies; but how they compare with daily treatment in relation to cure is unclear. Current international and national recommendations differ on use of intermittent regimens to treat TB in children. This review compares the efficacy and safety of intermittent, short-course anti-TB regimens (twice- or thrice-weekly) with daily short-course anti-TB regimens in treating childhood TB

Summary: About half a million children are diagnosed with tuberculosis (TB) every year, usually infecting the lungs, but also other organs of the body, and can cause meningitis. Infection in children is relatively common, and so establishing effective drug regimens that are easy to take and monitor is important.

TB drug regimens are standardised globally, and include a combination of drugs given daily for six months. More than 95% of children are cured with this treatment. Giving anti-TB drugs twice- or thrice-weekly is more convenient to supervise than daily treatment but may not be as effective as daily treatment in curing children of TB. The World Health Organization currently recommends only daily treatments, but some national governments recommend twice- or thrice-weekly doses for children with TB.

In this Cochrane review, the review authors compared children given intermittent anti-TB treatment to those given daily treatment. They examined the evidence up to 30 May 2013 and included four randomized trials that compared twice-weekly treatment with daily doses of anti-TB drugs, but none evaluated thrice-weekly dosing. The four trials included 563 children aged five months to 15 years, not known to be resistant to TB drugs. The trials were published over 12 years ago and the regimens used are not those currently recommended.

The trials were small, and did not detect a difference between twice-weekly or daily treatment in the number of children who were cured, died, relapsed, reported taking most or all of the drugs, or had adverse effects. Whether regimens of drugs two or three times a week are as good as regimens with daily doses remains unclear, as the evidence base to date is small, and the regimens tested are not the same as currently recommended drug combinations.

Citation: Bose A, Kalita S, Rose W, Tharyan P. Intermittent versus daily therapy for treating tuberculosis in children. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD007953. DOI: 10.1002/14651858.CD007953.pub2

Treating BCG-induced disease in children

Bacillus Calmette-Guérin (BCG) is a live attenuated vaccine to prevent tuberculosis, routinely administered at birth as part of the World Health Organization global expanded immunisation programme. Given intradermally, it can cause adverse reactions, including local, regional, distant and disseminated manifestations that may cause parental distress. Rarely, it can cause serious illness and even death. Among those patients with immunocompromised conditions, such as the human immunodeficiency virus (HIV) infection, the complication rate is even higher. This review assesses the effects of different interventions for treating BCG-induced disease in children.

Summary: Bacillus Calmette-Guérin (BCG) is a widely used tuberculosis vaccine derived from a non-infectious strain of the bovine tuberculosis bacillus (*Mycobacterium bovis*) and mainly given to young children. Usually, the only adverse reaction to the vaccine is an ulcer at the site of injection, which may leave a small scar.

Very occasionally, however, especially in children with weakened immune systems, the vaccine can cause more serious side effects. These can include local infections at the injection site, which may spread to the lymph nodes, causing lymphadenopathy, and the bones, and can even prove life-threatening. These adverse reactions to the BCG vaccine are a particular risk for children infected with the Human Immunodeficiency Virus (HIV), where the condition is known as BCG immune reconstitution inflammatory syndrome (BCG-IRIS).

In many cases, the infections resolve without any intervention, but treatments can include oral antibiotics, needle aspiration, draining abscesses, and surgically removing infected lymph nodes. This review was conducted to try to determine the effectiveness of these different treatments.

The review found no evidence of any benefit of using oral antibiotics to treat local or regional BCG-induced disease. In patients with abscess-forming lymphadenopathy, the only intervention with proven benefit was needle aspiration of the abscesses with or without local injection of the antibiotic isoniazid.

Based on these findings, the review authors recommend a 'wait and see' approach with follow-up visits for minor reactions and lymphadenopathy without abscesses. For abscess-forming lymphadenopathy, which can cause distress and discomfort, they advise needle aspiration. However, this review is based on only five studies, all of which were assessed as having a low or very low quality of evidence. As a consequence, the authors conclude there is an urgent need for more and better studies on ways to prevent and treat BCG-induced disease, especially BCG-IRIS.

Citation: Cuello-García CA, Pérez-Gaxiola G, Jiménez Gutiérrez C. Treating BCG-induced disease in children. *Cochrane Database of Systematic Reviews* 2013, Issue 1. Art. No.: CD008300. DOI: 10.1002/14651858.CD008300.pub2

Mycobacterium vaccae immunotherapy for treating tuberculosis

Some authorities have advocated Mycobacterium vaccae immunotherapy for treating tuberculosis and other infections caused by mycobacteria. This review evaluates M. vaccae immunotherapy as an adjunct to chemotherapy for people with tuberculosis.

Summary: Injections that aim to influence a person's immune system have been used by doctors to lessen the chance of a person developing a disease, or sometimes to reduce the damage the disease does to the body. *M. vaccae* is a type of bacterium related to the one that causes tuberculosis. Scientists have wondered if injections of this could reduce the damage done to someone when they are infected with tuberculosis, and some early trials suggested this might be true. However, this overview involving eight trials identified that the research does not show any consistent effect of this injection on death or the course of tuberculosis illness. It may be that the early trials had methodological problems that led to false optimism about this intervention.

Citation: de Bruyn G, Garner P. *Mycobacterium vaccae* immunotherapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD001166. DOI: 10.1002/14651858.CD001166

Rifabutin for treating pulmonary tuberculosis

Rifamycins are an essential component of modern short-course regimens for treating tuberculosis. Rifabutin has favourable pharmacokinetic and pharmacodynamic properties and is less prone to drug-drug interactions than rifampicin. It could contribute to shortening of therapy or simplify treatment in human immunodeficiency virus (HIV)-positive people who also need antiretroviral drugs. This review compares combination drug regimens containing rifabutin with those containing rifampicin for treating pulmonary tuberculosis.

Summary: Among current challenges in tuberculosis treatment are reducing the length of time that drugs must be taken to less than six months and finding ways to safely combine tuberculosis drugs with those used in the treatment of HIV infection. Rifabutin is a drug that has the potential to address these issues if substituted for rifampicin, a mainstay of current treatment. This review identified five trials involving 924 people, but none were of high quality. The review found no

significant differences between rifabutin- and rifampicin-containing treatment in curing tuberculosis and preventing relapse, but higher doses of rifabutin might be associated with more adverse effects and there was no evidence that it could shorten treatment. However, very few people with HIV and tuberculosis, who are most likely to benefit from use of rifabutin due to its lack of interaction with antiretroviral drugs, were included in the trials. Better quality clinical trials are needed to understand the place of rifabutin in the treatment of people with tuberculosis, particularly those who also have HIV.

Citation: Davies GR, Cerrri S, Richeldi L. Rifabutin for treating pulmonary tuberculosis. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005159. DOI: 10.1002/14651858.CD005159.pub2

Corticosteroids for tuberculous pleurisy

Corticosteroids used in addition to antituberculous therapy have been reported to benefit people with tuberculous pleurisy. However, research findings are inconsistent, raising doubt as to whether such treatment is worthwhile. Concern also exists regarding the potential adverse effects of corticosteroids, especially in HIV-positive people. This review evaluates the effects of adding corticosteroids to drug regimens for tuberculous pleural effusion.

Summary: Tuberculous pleural effusion results from tuberculous infection of the membrane covering of the lungs. This results in a build up of fluid around the lung that impairs breathing and may lead to restriction of lung function in the long term. Some clinicians believe that corticosteroids used in combination with antituberculous drugs can help to prevent these complications. We found no clear evidence supporting the use of corticosteroids in people with tuberculous pleural effusion, regardless of HIV status. However, only one trial evaluated the balance between benefit and harm of corticosteroids in people infected with HIV.

Citation: Engel ME, Matchaba PT, Volmink J. Corticosteroids for tuberculous pleurisy. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD001876. DOI: 10.1002/14651858.CD001876.pub2

Corticosteroids for managing tuberculous meningitis

Tuberculous meningitis, a serious form of tuberculosis that affects the meninges covering the brain and spinal cord, is associated with high mortality and disability among survivors. Corticosteroids have been used as an adjunct to antituberculous drugs to improve the outcome, but their role is controversial. This review will evaluate the effects of corticosteroids as an adjunct to antituberculous treatment on death and severe disability in people with tuberculous meningitis.

Summary: Tuberculous meningitis is a serious form of tuberculosis affecting the meninges covering the brain and spinal cord. The clinical outcome is poor even when treated with conventional antituberculous drugs. Corticosteroids are commonly used in addition to antituberculous drugs for treating the condition. They help reduce swelling and congestion of the meninges, and thus decrease pressure inside the brain and the attendant risk of death or disabling residual neurological deficit among survivors. This review identified seven trials involving 1140 people that evaluated either dexamethasone or prednisolone given in addition to antituberculous drugs; only one trial was of high quality. Overall, the trials showed that corticosteroids help reduce the risk of death or a risk of death or disabling residual neurological deficit. Only one trial evaluated the effects of corticosteroids in HIV-positive people, but the effects were unclear. Given the results of the review, all HIV-negative people with tuberculous meningitis should receive corticosteroids, but more trials are needed in HIV-positive people.

Citation: Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD002244. DOI: 10.1002/14651858.CD002244.pub3

Fluoroquinolones for treating tuberculosis

Fluoroquinolones are sometimes used to treat multiple-drug-resistant and drug-sensitive tuberculosis. This review assesses fluoroquinolones as additional or substitute components to antituberculous drug regimens for drug-sensitive and drug-resistant tuberculosis.

Summary: Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* bacteria. Over two billion people worldwide are believed to be latently infected with TB and approximately 10% of these people will develop active TB later in life. The World Health Organization currently only recommend treatment with fluoroquinolones for patients who cannot take standard first-line drugs. In this review, we examined the effect of including fluoroquinolones in first-line treatment regimens on people with presumed drug-sensitive tuberculosis.

We examined the research published up to 6 March 2013 and we identified five randomised controlled trials (1330 people) that met the inclusion criteria. The trials were performed in low- and middle-income countries located in geographically diverse areas but there was a lack of studies conducted in Asia. We found no studies that examined the effect of including fluoroquinolones in a standard six month TB treatment regimen on treatment failure. We do not know whether adding fluoroquinolones or substituting fluoroquinolones for ethambutol in a standard six month TB treatment regimen reduces treatment failure, relapse, death, or adverse events. Substituting fluoroquinolones for isoniazid in a standard six month TB treatment regimen may have little or no difference upon death and adverse events. Currently, there are nine randomised controlled trials ongoing.

HIV-positive participants were relatively well-represented in the included trials but none of the included trials stratified outcomes by HIV status. Also, the primary outcomes of all the included trials were reached before initiation of antiretroviral treatment. Evidence is generally lacking on the safety and efficacy of fluoroquinolone additions or substitutions in children (< 18 years) and in pregnant and lactating women.

Citation: Ziganshina LE, Titarenko AF, Davies GR. Fluoroquinolones for treating tuberculosis (presumed drug-sensitive). Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD004795. DOI: 10.1002/14651858.CD004795.pub4

Fully intermittent dosing with drugs for treating tuberculosis in adults

The number of people infected with tuberculosis continues to rise worldwide. Rifampicin-containing treatment regimens can achieve high cure rates. Intermittent drug treatment delivered in the community has the potential to improve adherence to treatment. This review compares the effectiveness of rifampicin-containing short-course chemotherapy regimens, given two or three times a week, with similar regimens given daily in adult patients with pulmonary tuberculosis.

Summary: Rifampicin-containing drug combinations can achieve high cure rates in patients with pulmonary tuberculosis when given for six months. Such treatment can be given either daily or intermittently (eg three times a week) from the beginning. This review compared the equivalence of effect between such treatments but did not find enough evidence to be able to assess this.

Citation: Mwandumba HC, Squire SB. Fully intermittent dosing with drugs for treating tuberculosis in adults. Cochrane Database of Systematic Reviews 2001, Issue 4. Art. No.: CD000970. DOI: 10.1002/14651858.CD000970

Interventions for treating tuberculous pericarditis

Tuberculous pericarditis – tuberculosis infection of the pericardial membrane (pericardium) covering the heart – is becoming more common. The infection can result in fluid around the heart or fibrosis of the pericardium, which can be fatal. The review evaluates, in people with tuberculous pericarditis, the effects on death, life-threatening conditions, and persistent disability of six-month antituberculous drug regimens compared with regimens of nine months or more; corticosteroids; pericardial drainage; and pericardiectomy.

Summary: Currently doctors prescribe antituberculous drugs and remove the membrane if it is making the patient ill. However, doctors vary in the way they manage this condition in terms of what antituberculous drugs to give and when to operate. We found no clinical trials that tackled the length of anti-TB treatment needed. Trials of steroids given with antituberculous drugs suggest possible benefit, but this was not demonstrated conclusively. Open surgical drainage of the fluid accumulating between the heart and the membrane using general anaesthesia was associated with less life threatening re-accumulation of fluid (cardiac tamponade), but with more deaths, but conclusions are not possible as the numbers of patients studied was too small.

Citation: Mayosi BM. Interventions for treating tuberculous pericarditis. Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD000526. DOI: 10.1002/14651858.CD000526

Treatment of latent tuberculosis infection in HIV infected persons

Individuals with human immunodeficiency virus (HIV) infection are at an increased risk of developing active tuberculosis. It is known that treatment of latent tuberculosis infection (LTBI), also referred to as tuberculosis preventive therapy or chemoprophylaxis, helps to prevent progression to active disease in HIV-negative populations. However, the extent and magnitude of protection (if any) associated with preventive therapy in those infected with HIV should be quantified. This review determines the effectiveness of tuberculosis preventive therapy in reducing the risk of active tuberculosis and death in HIV-infected people.

Summary: Most people infected with tuberculosis (TB) never get TB symptoms. This is called latent TB. People infected with HIV/AIDS are at increased risk of getting TB and about 30% of people with HIV who have latent TB will eventually get active TB. This results in an increase in the risk of earlier death. This update of the review of available clinical trials found that the risk of developing active TB was reduced when people infected with both HIV and TB used isoniazid. Isoniazid for latent TB is usually taken for six to 12 months, but more research is still needed to show optimal duration of treatment, the best treatment regime for people with HIV, and especially the best regimen in combination with HIV drugs.

Citation: Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD000171. DOI: 10.1002/14651858.CD000171.pub3

Other types of treatment, including nutrition

Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Tuberculosis is generally curable with chemotherapy, but there is controversy in the literature about the need for surgical intervention in the one to two per cent of people with tuberculosis of the spine. This review compares chemotherapy plus surgery with chemotherapy alone for treating people diagnosed with active tuberculosis of the spine.

Summary: Spinal tuberculosis (spinal TB) occurs in about 1% to 2% of people with TB (the most common infectious disease in the world). The disease can have a major impact on people's lives. Nerves can be squeezed causing pain, loss of feeling, and breathing problems. It can cause bone loss and curvature of the spine, which can lead to loss of nerve function and paralysis after some years, even if the TB has been cured. Correcting with surgery at this point can be difficult because of the complexity of the surgery required. It has been suggested that surgery might be undertaken at the time the TB of the spine is diagnosed and drug treatment (chemotherapy) is being used. However, all surgery has potential adverse effects. This review of trials found there were insufficient numbers of participants in the two trials located (331 participants) to be able to say if routine surgery early on was of overall benefit. Further trials are needed and such trials should assess the pain that people suffer and their views of the disease and treatment.

Citation: Jutte PC, van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004532. DOI: 10.1002/14651858.CD004532.pub2

Low level laser therapy for treating tuberculosis

The main treatment for tuberculosis is antituberculous drugs. Low level laser therapy is used as an adjunct to antituberculous drugs, predominantly in the former Soviet Union and India. This review compares low level laser therapy plus antituberculous drugs with antituberculous drugs alone for treating tuberculosis.

Summary: Tuberculosis (TB) is a serious bacterial infection that can affect different parts of the body; most frequently it affects the lungs (pulmonary TB). Some bacteria can be drug resistant, and some people may have the infection alongside another medical condition. People suffer from severe cough, weakness and sweats, and some people still die from TB even though effective drug treatment has been around for many years. It has been proposed that low level laser therapy may help the drugs to be more effective. There are a number of different devices for giving the laser treatment, some giving the treatment externally (to the body or acupuncture sites), some using for internal treatment (for blood or lungs) at varying doses. The review of trials found only one randomized trial where the data were poorly reported, and it did not clarify the potential benefits and harms. Low level laser therapy should only be used in randomized controlled trials until its value is evaluated

Citation: Vlassov VV, Reze AG. Low level laser therapy for treating tuberculosis. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD003490. DOI: 10.1002/14651858.CD003490.pub2

Nutritional supplements for people being treated for active tuberculosis

Tuberculosis and malnutrition are linked in a complex relationship. The infection may cause under-nutrition through increased metabolic demands and decreased intake, and nutritional deficiencies may worsen the disease, or delay recovery by depressing important immune functions. At present, there are no evidence-based nutritional guidance for adults and children being treated for tuberculosis. This review assesses the effects of oral nutritional supplements (food, protein/energy supplements or micronutrients) on tuberculosis treatment outcomes and recovery in people on antituberculous drug therapy for active tuberculosis.

Summary: Researchers in The Cochrane Collaboration conducted a review of the effects of nutritional supplements for people being treated for tuberculosis. After searching for relevant studies, they identified 23 relevant articles. Their findings are summarized below.

What is tuberculosis and how might nutritional supplements work?

Tuberculosis is a bacterial infection which most commonly affects the lungs. Most people who get infected never develop symptoms as their immune system manages to control the bacteria. Active tuberculosis occurs when the infection is no longer contained by the immune system, and typical symptoms are cough, chest pain, fever, night sweats, weight loss, and sometimes coughing up blood. Treatment is with a combination of antibiotic drugs, which must be taken for at least six months.

People with tuberculosis are often malnourished, and malnourished people are at higher risk of developing tuberculosis as their immune system is weakened. Nutritional supplements could help people recover from the illness by strengthening their immune system, and by improving weight gain, and muscle strength, allowing the patient to return to an active life.

Good nutrition requires a daily intake of macronutrients (carbohydrate, protein, and fat), and micronutrients (essential vitamins and minerals).

What the research says:

Effect of providing nutritional supplements to people being treated for tuberculosis

We currently don't know if providing free food to tuberculosis patients, as hot meals or ration parcels, reduces death or improves cure. Providing free food probably does improve weight gain during treatment, and may improve quality of life but further research is necessary.

We don't know if vitamins reduce death in HIV-negative people but they probably don't work in HIV-positive people with tuberculosis. No studies have assessed whether vitamins improve tuberculosis cure. Vitamins probably don't improve weight gain, and no studies have assessed their effect on quality of life.

Citation: Sinclair D, Abba K, Grobler L, Sudarsanam TD. Nutritional supplements for people being treated for active tuberculosis. Cochrane Database of Systematic Reviews 2011, Issue 11. Art. No.: CD006086. DOI: 10.1002/14651858.CD006086.pub3

Delivery strategies

Patient education and counselling for promoting adherence to treatment for tuberculosis

Non-adherence to tuberculosis treatment can lead to prolonged periods of infectiousness, relapse, emergence of drug-resistance, and increased morbidity and mortality. This review assesses whether patient education or counselling, or both, promotes adherence to tuberculosis treatment.

Summary: Many people do not take their medication as prescribed. The consequences of this for chronic and debilitating infections like tuberculosis are serious and can include prolonged periods of infectiousness, relapse, emergence of drug-resistant *Mycobacterium tuberculosis* isolates, and increased morbidity and mortality. Our review considered trials of education and counselling in promoting adherence to the treatment of both latent (dormant) and active tuberculosis.

We identified three very low quality evidence trials involving a total of 1437 participants that evaluated education and counselling interventions in promoting adherence to completion of medication for treatment of latent tuberculosis. Two of these studies demonstrated a beneficial effect of education and counselling upon adherence to drug treatment, whereas one did not.

There were substantial differences between trials with respect to populations targeted, interventions chosen and outcomes measured. The existing evidence is insufficient to guide policy on the use of education and counselling to promote adherence to tuberculosis therapy.

Citation: M'Imunya JM, Kredt T, Volmink J. Patient education and counselling for promoting adherence to treatment for tuberculosis. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD006591. DOI: 10.1002/14651858.CD006591.pub2

Directly observed therapy for treating tuberculosis

For tuberculosis treatment, policies have been introduced to encourage adherence to treatment regimens. One such policy is directly observed therapy (DOT), which involves people directly observing patients taking their antituberculous drugs. This review compares DOT with self administration of treatment or different DOT options for people requiring treatment for clinically active tuberculosis or prevention of active disease.

Summary: Tuberculosis is a very serious health problem with two million people dying each year, mostly in low-income countries. Effective drugs for tuberculosis have been available since the 1940s, but the problem still abounds. People with tuberculosis need to take the drugs for at least six months, but many do not complete their course of treatment. For this reason, services for people with tuberculosis often use different approaches to encourage people to complete their course of treatment. This review found no evidence that direct observation by health workers, family members, or community members of people taking their medication showed better cure rates than people having self administered treatment. The intervention is expensive to implement, and there appears to be no sound reason to advocate its routine use until we better understand the situations in which it may be beneficial.

Citation: Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003343. DOI: 10.1002/14651858.CD003343.pub3

Material incentives and enablers in the management of tuberculosis

Patient adherence to medications, particularly for conditions requiring prolonged treatment such as tuberculosis, is frequently less than ideal, and can result in poor treatment outcomes. Material incentives (given as cash, vouchers and tokens), have been used to improve adherence. This review assesses the effects of material incentives in people undergoing diagnostic testing, or receiving prophylactic or curative therapy, for tuberculosis.

Summary: Patients do not always follow the advice of health care providers if being investigated or treated for tuberculosis. Material incentives (such as cash, vouchers and tokens) may encourage them to return for the results of tests or to take prescribed treatments. This review, which analysed the results of 11 randomized controlled trials, concluded that material incentives do increase the number of patients (in certain marginalized subpopulations, mostly men) who return to the clinic to receive their test results for the diagnosis of tuberculosis, and the number of patients who go to the clinic to start treatment for tuberculosis. There was no evidence to show that incentives increase the number of patients who complete treatment for latent or active tuberculosis.

Citation: Lutge EE, Wiysonge CS, Knight SE, Volmink J. Material incentives and enablers in the management of tuberculosis. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD007952. DOI: 10.1002/14651858.CD007952.pub2

Reminder systems and late patient tracers in the diagnosis and management of tuberculosis

Reminder systems and late patient tracers as strategies to improve patients' adherence to tuberculosis screening, diagnosis, and treatment are used in some countries, but their effectiveness has not previously been systematically reviewed. This review assesses the effects of reminder systems and late patient tracers on a range of outcomes relating to the diagnosis and management of tuberculosis. These include completion of diagnostics, commencement of treatment in people referred for curative or prophylactic treatment of tuberculosis, completion of treatment in people starting curative or prophylactic treatment for tuberculosis, and cure in people being treated for active tuberculosis.

Summary: This review aimed to assess the effects of reminder systems and late patient tracers on patients' adherence to medical advice (such as attending clinic appointments for taking anti-tuberculosis drugs) and on clinical outcomes (such as cure of tuberculosis) in the following situations: treatment for active tuberculosis; tests for diagnosis of tuberculosis; and treatment to prevent tuberculosis in high-risk individuals. Reminder systems are used before a clinic or drug-collection appointment to remind patients to attend the appointment, or sometimes during treatment at home to remind patients to take their drugs. Late patient tracers are similar interventions undertaken when patients fail to keep an appointment to encourage them to return to treatment. The review found nine trials involving 5257 participants. Six trials assessed reminder systems and three trials assessed the use of late patient tracers. The results from five of the six reminder trials showed benefits. Trials of late patient tracers (home visits and letters) also showed benefits of the intervention in increasing adherence to tuberculosis treatment. Hence, overall, the results showed better outcomes among those patients for whom reminders or late patient tracers were used.

Citation: Liu Q, Abba K, Alejandria MM, Balanag VM, Berba RP, Lansang MAD. Reminder systems and late patient tracers in the diagnosis and management of tuberculosis. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD006594. DOI: 10.1002/14651858.CD006594.pub2

Active case finding in contacts of people with tuberculosis

Tuberculosis is a major global health challenge that is caused by bacteria which is spread by airborne droplets. Mostly patients are identified in high-burden countries when they visit health care facilities ('passive case finding'). Contacts of tuberculosis patients are a high-risk group for developing the disease. Actively screening contacts of people with confirmed tuberculosis may improve case detection rates and control of the disease. This review aims to compare whether active case finding among contacts of people with confirmed tuberculosis increases case detection compared to usual practice.

Summary: Tuberculosis is a serious infectious disease that affects over nine million people each year. The disease is spread by airborne droplets, which arise in the infected lungs of tuberculosis patients. Despite widespread availability of treatment with effective antibiotic therapies, the disease remains common in many resource limited settings. This review aimed to determine whether systematic screening all the direct contacts with people with proven TB disease increases the early detection of tuberculosis. The review found that there are not currently any suitable randomized controlled trials to answer this question and there is insufficient evidence to show whether screening programmes for tuberculosis will improve the rate of diagnosis among contacts of tuberculosis patients or reduce the rate of tuberculosis in the community. Therefore there is a need for further research to determine the benefits of systematic screening of the contacts of tuberculosis patients.

Citation: Fox GJ, Dobler CC, Marks GB. Active case finding in contacts of people with tuberculosis. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD008477. DOI: 10.1002/14651858.CD008477.pub2

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