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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	7
Figure 1.	8
Figure 2.	9
Figure 3.	10
DISCUSSION	11
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	13
REFERENCES	13
CHARACTERISTICS OF STUDIES	14
DATA AND ANALYSES	20
Analysis 1.1. Comparison 1 Isoniazid versus no treatment, Outcome 1 Tuberculosis.	20
Analysis 1.2. Comparison 1 Isoniazid versus no treatment, Outcome 2 All-cause mortality.	21
Analysis 1.3. Comparison 1 Isoniazid versus no treatment, Outcome 3 Isoniazid hepatotoxicity.	22
Analysis 1.4. Comparison 1 Isoniazid versus no treatment, Outcome 4 Rejection episodes.	22
APPENDICES	22
CONTRIBUTIONS OF AUTHORS	26
DECLARATIONS OF INTEREST	26
SOURCES OF SUPPORT	27
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	27
INDEX TERMS	27

Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis

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ABSTRACT

Background

Organ transplant recipients are at increased risk of infection as a result of immunosuppression caused inadvertently by medical treatment. Tuberculosis (TB) is a challenging infection to manage among organ transplant recipients that can be transmitted from infected people or triggered from latent infection. Organ transplant recipients have been reported to be up to 300 times more likely to develop TB than the general population. Consensus about the use of antibiotic prophylaxis to prevent post solid organ transplant TB has not been achieved.

Objectives

This review assessed the benefits and harms of antibiotic prophylaxis to prevent post solid organ transplant TB.

Search methods

We searched the Cochrane Renal Group's Specialised Register up to 30 April 2013 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. Studies contained in the Specialised Register are identified through search strategies specifically designed for CENTRAL, MEDLINE and EMBASE and handsearching conference proceedings.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs that compared antibiotic prophylaxis with a placebo or no intervention for recipients of solid organ transplants were included.

Data collection and analysis

Two authors independently assessed studies for inclusion and extracted data. We derived risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data with 95% confidence intervals (CI). Methodological risk of bias was assessed using the Cochrane risk of bias tool.

Main results

We identified three studies (10 reports) that involved 558 kidney transplant recipients which met our inclusion criteria. All studies were conducted in countries that have high prevalence of TB (India and Pakistan), and investigated isoniazid, an oral antibacterial drug. Control in all studies was no antibiotic prophylaxis. Prophylactic administration of isoniazid reduced the risk of developing TB post-transplant (3 studies, RR 0.35 95% CI 0.14 to 0.89), and there was no significant effect on all-cause mortality (2 studies, RR 1.39, 95% CI 0.70 to 2.78). There was however substantial risk of liver damage (3 studies, RR 2.74, 95% CI 1.22 to 6.17).

Reporting of methodological quality parameters was incomplete in all three studies. Overall, risk of bias was assessed as suboptimal.

Authors' conclusions

Isoniazid prophylaxis for kidney transplant recipients reduced the risk of developing TB post-transplant. Kidney transplant recipients in settings that have high prevalence of TB should receive isoniazid during the first year following transplant. There is however, significant risk of liver damage, particularly among those who are hepatitis B or C positive. Further studies are needed among recipients of other solid organ transplants and in settings with low prevalence of TB to determine the benefits and harms of anti-TB prophylaxis in those populations.

PLAIN LANGUAGE SUMMARY

Which drugs are most effective to prevent tuberculosis in organ transplant recipients?

Organ transplantation is often the best treatment option for patients with end-stage kidney, pancreas, heart, liver and lung disease. A major risk for transplant recipients is organ rejection. Although anti-rejection drugs improve survival, they weaken the immune system and increase the risk of infection, cancer, and cardiovascular disease.

Preventing and managing infection is a major challenge in organ transplant recipients. Tuberculosis (TB) is a particular concern because organ transplant recipients are up to 300 times more likely to contract this infection than people in the general population. TB can be difficult to diagnose because it can develop in different organs and body tissues aside from lungs.

We investigated whether drugs to prevent TB after transplant could reduce the disease in the post-transplant period. We found three studies that looked at 558 kidney transplant recipients in India and Pakistan where TB rates are high.

We found that taking the drug isoniazid (a tablet) during the first year after kidney transplant provided protection against developing TB. However, this drug also significantly increased the risk of liver damage. Most drug-related liver damage occurred in people who already had liver problems caused by hepatitis B or C. We also found that there was no difference in numbers of deaths from any cause between those who received the anti-TB drug and those who did not.

Although we found that isoniazid should be given to kidney transplant recipients in areas where TB is known to be a risk, further studies are needed in people who have received other organ transplants such as liver, lungs and heart, and where TB rates are low, to determine the wider benefits and harms of anti-TB drugs.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Isoniazid versus no treatment for preventing post solid organ transplant tuberculosis						
Patient or population: kidney transplant recipients Settings: hospital Intervention: isoniazid versus no treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Isoniazid				
Tuberculosis Follow-up: 2 to 4 years	Study population		RR 0.35 (0.14 to 0.89)	558 (3)	⊕⊕⊕○ moderate ¹	All studies conducted in kidney transplant population
	159 per 1000	45 per 1000 (22 to 86)				
	Moderate					
	259 per 1000	80 per 1000 (40 to 149)				
INH hepatotoxicity Jaundice, elevated bilirubin, elevated liver enzymes Follow-up: 2 to 4 years	Study population		RR 1.59 (1.06 to 2.40)	558 (3)	⊕⊕⊕○ moderate ²	Almost all reported hepatotoxicity (45/47) were from one study which had high prevalence of patients with hepatitis B and C infection
	58 per 1000	145 per 1000 (70 to 277)				
	Moderate					
	0 per 1000	0 per 1000 (0 to 0)				
All-cause mortality Follow-up: 2 to 4 years	Study population		RR 1.39 (0.7 to 2.78)	558 (3)	⊕⊕○○ low ^{2,3}	One of the three studies (largest study) reported no mortality

	32 per 1000	45 per 1000 (23 to 90)
	Moderate	
	0 per 1000	0 per 1000 (0 to 0)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

¹ All included studies were open-label with potential risk of detection and performance bias

² All included studies were open-label with significant potential risk of detection and performance bias

³ Deaths may not be directly related to prophylaxis

BACKGROUND

Description of the condition

Since the first successful kidney transplant in 1954, solid organ (kidney, liver, heart, lung, pancreas) transplantations have become the treatment of choice for many patients with organ failure. With the advent of newer, more effective and selective immunosuppressants, allograft and patient survival have increased, leaving infection and malignancy as the major barriers to disease-free survival (Fishman 2013).

Tuberculosis (TB) is a global health problem. There were an estimated 9.27 million new cases worldwide in 2007 (WHO 2009). Solid organ transplant recipients are up to 300 times more likely to develop TB than the general population (Roman 2000). TB incidence among solid organ transplant recipients varies according to geographic location, reflecting prevalence in the general population. In kidney transplant recipients, TB rates of 0.5% to 1.0% have been reported in North America, 0.7% to 5% in Europe, and 5% to 15% in India and Pakistan (EBPG 2002; Jha 2002).

Reactivation of quiescent infection is the most common source of TB infection in immunocompromised post-transplant organ transplant recipients (KDIGO 2009), but transmission from infected grafts or actively-infected people are also common (Singh 1998). More potent immunosuppressant regimes, such as tacrolimus and mycophenolate mofetil, have been associated with TB development earlier in the transplant period (Atasever 2005). Diagnosis of active TB is confirmed by the presence of acid-fast bacilli growth in culture media, demonstration of caseating granulomata with or without acid-fast bacilli in histological specimens, and more recently, polymerase chain reaction (PCR) (Malhotra 2007). Diagnosis of latent TB in transplant recipients requires induration of 5 mm on a tuberculin test (10 mm induration is required for the general population or people on dialysis) (EBPG 2002).

TB is associated with high morbidity and mortality in solid organ transplant recipients, among whom incidence of atypical and obscured presentations are also more common, leading to delayed diagnosis (Malhotra 2007). Incidence of disseminated infections (EBPG 2002) with attendant morbidity are more common and mortality rates are up to 10-fold greater than in immunocompetent people with TB (KDIGO 2009). Further challenges emanate from interactions between anti-TB drugs and immunosuppressants: rifampicin induces cytochrome P450 microenzymes, leading to reduced calcineurin inhibitor levels (Aguado 2009). This interaction was associated with a 30% incidence of graft rejection and 20% incidence of graft loss in one study (Singh 1998).

The European Best Practice Guidelines (EBPG) recommend antibiotic prophylaxis against TB for solid organ transplant recipients with latent TB. Presence of latent TB is defined by positive tuberculin reaction, chest X-ray suggestive of past TB, history of inadequately treated TB or close contact with TB patient (EBPG 2002).

The most widely used anti-TB prophylaxis drug post-transplant is isoniazid (300 mg daily or 25 mg/kg twice weekly) administered for six to nine months. Alternative therapies include daily rifampin/pyrazinamide for two months, or rifampin alone for four months (EBPG 2002). The American Society of Transplantation Guidelines for the Prevention and Management of Infectious Complications of Solid Organ Transplantation made similar recommendations for anti-TB prophylaxis post-transplant (Subramanian 2009). A consensus view has not however been achieved: the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest no differences in TB prophylaxis for kidney transplant recipients from the general population who need therapy (KDIGO 2009).

Tuberculin reactivity tests to identify people who should receive prophylaxis are limited because loss or suppression of normal immune response is common among people with end-stage kidney disease. Most people who develop TB post-transplant have negative tuberculin reactions pre-transplant. Klotz 2004 reported that 20% to 25% of all TB diagnosed following transplantation was in people who had positive tuberculin reactivity before transplantation. Techniques to detect latent TB, which could overcome the limitations of tuberculin reactivity, such as measurement of interferon gamma release in response to *Mycobacterium tuberculosis* antigens (QuantiFERON TB Gold Test), are being developed and validated. However, sensitivity and specificity of latent TB diagnostic tests have not yet been systematically evaluated in kidney transplant recipients. Data from people with stage 5 chronic kidney disease suggest limitations in detecting latent TB infection and their routine use are limited (KDIGO 2009). Universal prophylaxis against TB in solid organ transplant recipients remains controversial (Alexander 2012).

How the intervention might work

Most active TB in transplant recipients is thought to develop from reactivation of quiescent foci of *M. tuberculosis* that persist after initial infection earlier in life (latent TB) (EBPG 2002). Treatment of latent infection (prophylaxis for reactivation) could offer protection against active TB for solid organ transplant recipients, particularly during the peak immunosuppression period at six months to one year post-transplant.

Description of the intervention

Why it is important to do this review

Randomised controlled trials (RCTs) investigating antibiotics for TB prevention in post solid organ transplant recipients present some conflicting results (Agarwal 2004; Naqvi 2010). As yet, the side effect profiles of prophylactic drugs and their likelihood to interact with immunosuppressant drugs in transplant recipients have not been systematically assessed, and risk/benefit ratio data for antibiotic prophylaxis for latent TB are lacking. It is therefore important to systematically review published RCTs that investigate antibiotic prophylaxis in transplant recipients and to pool results to assess issues such as drug-related adverse events and interactions.

OBJECTIVES

We aimed to assess the benefits and harms of antibiotic prophylaxis for preventing TB in post solid organ transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) investigating antibiotic prophylaxis for preventing post solid organ transplant TB.

Types of participants

Inclusion criteria

1. Solid organ transplant recipients (i.e. lung, liver, heart, kidney, pancreas; single or multiple organs; cadaveric or living donors)
2. All ages and both genders.

Exclusion criteria

1. Study designs other than RCTs and quasi-RCTs
2. Non-solid organ transplants (e.g. intestine, bone marrow, stem cell).

Types of interventions

1. Any anti-TB antibiotic versus placebo, standard or no treatment
2. Comparison of any two or more anti-TB antibiotics.

Types of outcome measures

Primary outcomes

Occurrence of TB of any organ (confirmed by cultures of relevant samples, histology, Ziehl-Neelsen (acid-fast bacilli) staining or PCR).

Secondary outcomes

1. Acute allograft rejection (biopsy proven)
2. Chronic allograft rejection (biopsy proven)
3. Calcineurin toxicity (confirmed by biopsy or clinical diagnosis, i.e. in the setting of high calcineurin levels with high creatinine which improves calcineurin levels)
4. Unclassified allograft dysfunction
5. Kidney function measures (either end of treatment creatinine, change in creatinine, creatinine clearance, or all, as reported by primary authors)
6. Hepatitis (as reported by primary authors or specific liver function result)
7. Hospital admissions
8. Withdrawal from treatment
9. Mortality
10. Other adverse events as reported by primary authors of RCTs or quasi-RCTs (e.g. drug resistance, non-mycobacterial pneumonias).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register up to 30 April 2013 through contact with the Trials' Search Co-ordinator using search terms relevant to this review, without language restriction.

The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceed-

ings and current awareness alerts, are available in the specialised register section of information about the [Cochrane Renal Group](#). See [Appendix 1](#) for search terms used in strategies for this review.

Searching other resources

1. Reference lists of clinical practice guidelines review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies and other experts in the field.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that could be relevant to the review. Titles and abstracts were screened independently by two authors who discarded studies that were not applicable; however, studies and reviews that might include relevant data were retained initially. The same authors independently assessed retrieved abstracts, and if necessary the full text, of these studies and determined which satisfied the inclusion criteria. Disagreements were resolved in consultation with a third author.

Data extraction and management

Data extraction was carried out independently by two authors using standardised data extraction forms. Where more than one publication of one study existed, reports were grouped together and only the publication with the most complete data was used. Discrepancies between published versions were highlighted. Additional information required from original authors was requested by written correspondence and information obtained in this manner was included in the review. Disagreements were resolved in consultation with a third author.

Assessment of risk of bias in included studies

The following items were assessed using the risk of bias assessment tool ([Higgins 2011](#)) (see [Appendix 2](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
 - Participants and personnel
 - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?

- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous data (TB occurrence, all-cause mortality, liver toxicity), results were expressed as risk ratios (RR) with 95% confidence intervals (95% CI). For continuous data, we reported mean differences (MD) or standardised mean differences (SMD) with 95% confidence intervals (95% CI).

Dealing with missing data

Where relevant, original authors were contacted to obtain missing data. Data obtained in this way were included in the analysis. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population was carefully performed. Attrition rates, such as drop-outs, losses to follow-up and withdrawals were investigated.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test ([Higgins 2003](#)). I² values of 25%, 50% and 75% corresponding to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Although we planned to assess reporting biases by constructing funnel plots, the small number of included studies (3) meant this was not possible ([Higgins 2011](#)).

Data synthesis

Data were pooled using the random-effects model.

Subgroup analysis and investigation of heterogeneity

The planned subgroup analyses were not performed because of the small number of included studies, all of which were conducted in kidney transplant recipients.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of country of publication. We also carried out sensitivity analysis on the outcome of liver damage.

RESULTS

Description of studies

Results of the search

The search strategy identified 55 potentially relevant titles ([Figure 1](#)). After assessing the abstracts and removing duplicates and irrelevant records, we retrieved the full text of 12 records and assessed them for eligibility. After full text assessment we included three studies (10 reports) ([Agarwal 2004](#); [Naqvi 2010](#); [Vikrant 2005](#)) and excluded one study (two reports) ([John 1994](#)).

Figure 1. Study flow diagram

Included studies

Three studies were included ([Agarwal 2004](#); [Naqvi 2010](#); [Vikrant](#)

[2005](#)). A total of 558 kidney transplant recipients were enrolled (range 85 to 388 participants) and randomised to receive either anti-TB prophylaxis (isoniazid, 300 mg/d for 1 year) or no chemo-

prophylactic treatment. The studies were undertaken in India (Agarwal 2004; Vikrant 2005) and Pakistan (Vikrant 2005). There were more men than women enrolled in each study and the mean ages ranged from 30.9 to 35.8 years. All studies reported TB as their primary outcome and mortality and liver dysfunction were secondary outcomes. Follow-up ranged from one year (Agarwal 2004; Vikrant 2005) to four years (Naqvi 2010). See [Characteristics of included studies](#).

Excluded studies

The relatively small yield of records for this review meant that the number of excluded studies was also small. John 1994 (two

reports) was excluded because of incomplete data: numbers who underwent kidney transplantation were not reported. The study also reported a significant attrition rate; over 50% of participants did not complete the study. Our efforts to contact the authors to clarify these issues were unsuccessful. Inclusion of this study would have introduced an unknown number of participants who were dialysis rather than transplant patients. See [Characteristics of excluded studies](#).

Risk of bias in included studies

Reporting of methodological quality parameters was incomplete in all three studies (Figure 2; Figure 3). Overall, risk of bias was assessed as suboptimal.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agarwal 2004	?	?	-	+	+	+
Naqvi 2010	+	?	-	-	+	?
Vikrant 2005	+	-	-	+	+	+

Allocation

Random sequence generation

One study ([Vikrant 2005](#)) used computer generated randomisation and one used random number tables ([Naqvi 2010](#)). Randomization method was not specified in [Agarwal 2004](#).

Allocation concealment

None of the studies reported allocation concealment. Consequently, all were assessed to be at significant risk of selection bias.

Blinding

Because none of the included studies were designed to include placebo as a control, and were open-labelled, all had clear risk of performance and detection bias. Risk of performance bias was introduced by permitting clinical diagnoses of TB to be made without laboratory confirmation in all studies. However, numbers of participants with clinical diagnoses without laboratory confirmation was small.

Incomplete outcome data

Incomplete outcome data appeared to be absent in the [Agarwal 2004](#) and [Vikrant 2005](#) studies. However incomplete outcome data seems to be significant in [Naqvi 2010](#). The authors reported

480 patients recruited in an earlier report of their work in 2006, but only 400 patients were reported in the 2010 report, leaving 80 patients unaccounted for. In addition, no deaths were reported in this study cohort, which seemed unlikely in a large population (400) of kidney transplant recipients over a four-year period.

Selective reporting

There was no significant risk of reporting bias among the included studies; the authors reported the outcomes they pre-defined.

Other potential sources of bias

We did not identify any other potential sources of bias in the included studies.

Effects of interventions

See: [Summary of findings for the main comparison Isoniazid versus no treatment for preventing post solid organ transplant tuberculosis](#)

Tuberculosis

Participants who received anti-TB prophylaxis (isoniazid) were 65% less likely to develop TB compared with those who did not receive chemoprophylaxis ([Analysis 1.1](#) (3 studies, 558 participants): RR 0.35, 95% CI 0.14 to 0.89; $I^2 = 49\%$). This difference was statistically significant.

Mortality

There was no significant difference between isoniazid and no chemoprophylaxis for all-cause mortality ([Analysis 1.2](#) (3 studies, 558 participants): RR 1.39, 95% CI 0.7 to 2.78; $I^2 = 0\%$).

Adverse events

The risk of developing liver dysfunction among those who received anti-TB prophylaxis was 59% higher than those who received no chemoprophylaxis ([Analysis 1.3](#) (3 studies, 558 participants): RR 1.59, 95% CI 1.06 to 2.40; $I^2 = 0\%$). However, most reported instances of liver dysfunction were mild, reversible and did not warrant discontinuation of treatment.

Acute allograft rejection (biopsy-proven)

Only [Naqvi 2010](#) ([Analysis 1.4](#)) reported rejection episodes, although it is not clear whether they were biopsy-proven acute rejection episodes. There were no statistically significant differences between the treatment and control arms in terms of acute rejection episodes.

Withdrawal from treatment

This outcome was recorded in only one patient in [Agarwal 2004](#). There was no withdrawal from treatment in [Naqvi 2010](#). It is not clear how many withdrew from treatment in [Vikrant 2005](#)

Other outcomes

The following outcomes were not reported in any of the included studies:

- Chronic allograft rejection (biopsy proven)
- Calcineurin toxicity
- Unclassified allograft dysfunction
- Kidney function measures
- Hospital admission.

Sensitivity analyses

Based on country, we repeated the analyses excluding the study from Pakistan ([Naqvi 2010](#)) but there was no significant change in the results.

DISCUSSION

Summary of main results

A statistically significant lower risk of developing TB was reported among kidney transplant recipients who received anti-TB prophylaxis (isoniazid). However, liver dysfunction was statistically significant among participants who received anti-TB prophylaxis compared with people in the control groups. Most reported liver dysfunction was mild and transient; 45/47 events were reported by [Vikrant 2005](#) which included a significant proportion (~25%) of participants with hepatitis B or C infection. Sensitivity analysis excluding this study yielded no statistically significant difference in the incidence of anti-TB drug hepatotoxicity.

All-cause mortality was not significantly different between those who received anti-TB prophylaxis and those who did not.

Overall completeness and applicability of evidence

All included studies were conducted in kidney transplant recipients, and hence, there was a paucity of data relating to other solid organ transplants. Therefore, the benefits and harms of anti-TB (isoniazid) prophylaxis could not be extrapolated with certainty to other solid organ transplant populations. However, a systematic review of TB among liver transplant recipients ([Holty 2009](#)) suggested that isoniazid prophylaxis should be used for patients who are at risk of developing TB. [Holty 2009](#) recommended that

all liver transplant recipients should be tuberculin skin tested and regarded as having latent TB if positive.

Applicability of the findings of this review to countries where TB prevalence is low is also doubtful because the risk of developing TB is directly proportional to the prevalence of TB in the general population.

The applicability of the findings of this review to paediatric solid organ transplant recipients is also limited. This is particularly so since TB in the transplant population chiefly results from reactivation of latent infection, whereas TB in the paediatric population is mainly primary disease.

Quality of the evidence

The main limitation in study quality was lack of blinding. Participants, investigators and laboratory staff were not blinded. This aspect was assessed as introducing a high risk of detection and performance bias in the studies.

A further factor that impacted negatively on evidence quality was diagnosis of TB. In some cases, definitive diagnosis of *M. tuberculosis* infection was not established by culture, histology or PCR (Agarwal 2004; Naqvi 2010). Naqvi 2010 reported that only positive acid-fast bacilli smear was used or positive response to anti-TB therapy. Direct microscopy for acid-fast bacilli is not specific for *M. tuberculosis* because non-tubercular mycobacteria (including commensals in the respiratory tract) can yield positive acid-fast smear results (API 2006).

Diagnosis of TB based on clinical response to anti-TB drugs is also fraught with errors because anti-TB drugs, such as rifampicin, have broad antibiotic properties and can lead to clinical response in infections other than TB.

Assessment of the methodological qualities of the included studies are summarised in the risk of bias summary and depicted in Figure 2 and Figure 3.

Potential biases in the review process

We acknowledge that relevant studies published in developing countries, where TB prevalence is high, may not be represented in databases such as MEDLINE and EMBASE. However, the search of the Cochrane Renal Group's Specialised Register, which includes studies not indexed in some major bibliographic databases, reduced the risk of missing relevant studies. Publication bias therefore could not be excluded. We were unable to construct funnel plots to examine risk of publication bias because of the small number of included studies.

Agreements and disagreements with other studies or reviews

Overall our findings agree with a meta-analysis that found a possible benefit from anti-TB prophylaxis (isoniazid) to prevent post-transplant TB (RR 0.31, 95% CI 0.19 to 0.51) (Currie 2010).

There were some differences between Currie 2010 and our review. Currie 2010 included John 1994, which we excluded because although 184 patients were randomised in the dialysis period, fewer than 50% completed prophylaxis (73 patients); and the number of patients who underwent transplant was not reported. We were unsuccessful in our attempt to contact the authors to obtain transplanted patient data. A further difference was that Currie 2010 included data from Naqvi 2010 twice. This spuriously increased the number of participants to 709.

Although we found no RCTs in other solid organ transplant recipients for inclusion, the review by Holty 2009 of TB in liver transplant recipients also concluded that isoniazid prophylaxis was beneficial for people at risk of TB after liver transplantation.

AUTHORS' CONCLUSIONS

Implications for practice

We found limited evidence of suboptimal quality to support that anti-TB prophylaxis using isoniazid for kidney transplant recipients during the first sixth months to one year post-transplant reduced the risk of developing TB. We also found evidence that isoniazid use, especially in people with hepatitis B and hepatitis C, increased the risk of liver dysfunction. Based on our findings, anti-TB prophylaxis should be administered to all kidney transplant recipients in TB-endemic regions during the first year post-transplant. This suggestion is in addition to established TB prophylaxis guidelines for people with latent TB, irrespective of country of residence (EBPG 2002). Consideration should also be given to administering isoniazid as prophylaxis for people who live in low TB prevalence countries if they have history of living in high TB prevalence countries, since the potential risk of re-activation of TB remains.

Liver function should be monitored, especially in people who have existing liver disease.

Further studies are needed to explore the benefits and harms of anti-TB prophylaxis for recipients of liver, heart and lung transplants in countries with low prevalence of TB.

Current evidence suggests the use of isoniazid as an anti-TB prophylactic drug for solid organ transplant recipients until further studies are completed investigating other anti-TB prophylaxes.

Implications for research

Considering the global impact of TB, and that solid organ transplant recipients are at increased risk of infection, there were surprisingly few RCTs identified. There is need for studies in pop-

ulations of other solid organ transplant recipients such as heart, lung, and liver. Further studies are also warranted in kidney transplant recipients because the included studies were few in number and open-label study designs. Several outcomes of relevance and interest, such as rejection rates, allograft survival rates, calcineurin inhibitor toxicity, were not addressed in published studies.

Since all current evidence originated from the Indian subcontinent, consideration should be given to conducting studies elsewhere.

Studies in children are also required.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agarwal 2004

Methods	<ul style="list-style-type: none"> Study design: prospective, open-label RCT Study duration: enrolment from October 1998 to September 2000 Follow-up: weekly for 3 months; 2 weekly for the next 3 months; monthly for the last 6 months. Follow up concluded September 2003
Participants	<ul style="list-style-type: none"> Setting: single centre Country: India Inclusion criteria: kidney transplant recipients Number (treatment group/control group): 27/58 Mean age $\pm$ SD (years): treatment group (34.2 ± 12.1); control group (34 ± 10.8) Sex (males): treatment group (92.6%); control group (78%) Exclusion criteria: active TB; active hepatitis
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Isoniazid <ul style="list-style-type: none"> Dose and duration: 300 mg/d for 1 year or until TB developed Pyridoxine <ul style="list-style-type: none"> Dose and duration: 20 mg/d for 1 year or until TB developed <p>Control group</p> <ul style="list-style-type: none"> No anti-TB chemoprophylaxis
Outcomes	<ul style="list-style-type: none"> TB of any site Chronic liver disease Death Withdrawal from treatment
Notes	<ul style="list-style-type: none"> Funding source: NS Enrolment: 90 patients were recruited (treatment/control; 30/60); 5 (treatment/control; 3/2) were excluded due to early graft loss

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization mentioned, but method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not stated
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding - open-label study

Agarwal 2004 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; no losses reported
Selective reporting (reporting bias)	Low risk	No selective reporting
Other bias	Low risk	No additional sources of bias detected

Naqvi 2010

Methods	<ul style="list-style-type: none"> Study design: prospective, open-label RCT Study duration: enrolment from April 2001 to September 2004 Follow-up: weekly, two-weekly, monthly, second monthly, then three monthly according to the period post-transplant. Follow-up minimum period: 4 years
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Pakistan Inclusion criteria: kidney transplant recipients (all donors were living and related to the recipient) Number <ul style="list-style-type: none"> Enrolled (400); analysed (388 after drop outs/losses) Treatment group (181); control group (207) Mean age (years): treatment group (32.8); control group (33.1) Sex (M/F): treatment group (141/40); control group (160/47) Exclusion criteria: NR
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Isoniazid <ul style="list-style-type: none"> Dose and duration: 300 mg/d in patients weighing more than 35 kg and 5 mg/kg/d in patients with 35 kg body weight) for 1 year Pyridoxine <ul style="list-style-type: none"> Dose and duration: 50 mg/d for 1 year <p>Control group</p> <ul style="list-style-type: none"> No anti-TB chemoprophylaxis
Outcomes	<ul style="list-style-type: none"> TB Hepatotoxicity Death
Notes	<ul style="list-style-type: none"> Funding source: NS Addition data provided by study authors <ul style="list-style-type: none"> Randomization was done according to tables (reference of book given), it was unblinded. The reason for disparity in number of patients in two publications is, the study was designed in 1999, to register 500 transplant recipients, after going through all ethical review board process and etc, it got started in April 2001. Interim results in a conference which was Conference of Asian Society of Transplant in October 2005, all presentation made at conference were published in Transplant Proceeding in 2006, so

	was this study for the reason that results were so significant study terminated after the presentation. Later on paper was written after all registered cases completed follow up period for considerable duration. <ul style="list-style-type: none">Dead patients were only excluded from study if they died during first year post-transplant, which is also mentioned in methods, no patient died due to direct effect from tuberculosis infection.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sampling number tables
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	80 patients unaccounted for in the latest study
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Unclear risk	Unclear

Vikrant 2005

Methods	<ul style="list-style-type: none"> Study design: prospective, open-label RCT Study duration: April 2000 to June 2001 Follow-up period: twice weekly during dialysis. Following transplantation weekly follow-up for 3 months, two weekly for 3 months, then monthly for 6 months to June 2004
Participants	<ul style="list-style-type: none"> Setting: single centre Country: India Inclusion criteria: ESKD patients accepted for maintenance haemodialysis followed by kidney transplant aged > 14 years; donor grafts living (83), deceased (2) Number treatment group/control group: 54/55 Mean age $\pm$ SD (years): treatment group (30.9 $\pm$ 8.8); control group (35.8 $\pm$ 12.2) Sex (male): treatment group (85.2%); control group (83.6%) Exclusion criteria: current TB, on anti-TB therapy or who completed therapy in the preceding 6 months; active hepatitis, defined by raised bilirubin or raised alanine aminotransferase (ALT) > 5 times the upper limit of normal or both
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Isoniazid <ul style="list-style-type: none"> Dose: 300 mg/d (200 mg in patients with body weight < 50 kg); over 1 year

	or until TB developed <ul style="list-style-type: none"> Pyridoxine <ul style="list-style-type: none"> Dose: 20 mg/d at the time of initiating maintenance haemodialysis Control group <ul style="list-style-type: none"> No anti-TB chemoprophylaxis
Outcomes	<ul style="list-style-type: none"> TB Liver dysfunction Death
Notes	<ul style="list-style-type: none"> Funding source: NS. Additional information obtained from authors by email on methods: <ul style="list-style-type: none"> Randomization was computer based No allocation concealment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; lost to follow-up: 9/109 (8.26%); (treatment/control (5/4))
Selective reporting (reporting bias)	Low risk	No selective reporting
Other bias	Low risk	No additional sources of bias detected

NR - not stated; RCT - randomised controlled trial; TB - tuberculosis

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
John 1994	Study participants were randomised during the dialysis period while wait-listed for transplant. The study had a high drop-out rate (fewer than 50% completed prophylaxis). The authors did not state how many patients ultimately underwent kidney transplant. Efforts to contact the authors were unsuccessful

DATA AND ANALYSES

Comparison 1. Isoniazid versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tuberculosis	3	558	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.14, 0.89]
2 All-cause mortality	3	558	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.66, 2.70]
3 Isoniazid hepatotoxicity	3	558	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.06, 2.40]
4 Rejection episodes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Isoniazid versus no treatment, Outcome 1 Tuberculosis.

Review: Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis

Comparison: 1 Isoniazid versus no treatment

Outcome: 1 Tuberculosis

Analysis 1.2. Comparison 1 Isoniazid versus no treatment, Outcome 2 All-cause mortality.

Review: Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis

Comparison: 1 Isoniazid versus no treatment

Outcome: 2 All-cause mortality

Analysis 1.3. Comparison 1 Isoniazid versus no treatment, Outcome 3 Isoniazid hepatotoxicity.

Review: Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis

Comparison: 1 Isoniazid versus no treatment

Outcome: 3 Isoniazid hepatotoxicity

Analysis 1.4. Comparison 1 Isoniazid versus no treatment, Outcome 4 Rejection episodes.

Review: Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis

Comparison: 1 Isoniazid versus no treatment

Outcome: 4 Rejection episodes

APPENDICES

Appendix I. Electronic search strategies

DATABASE	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. MeSH descriptor Organ Transplantation, this term only 2. MeSH descriptor Heart Transplantation explode all trees 3. MeSH descriptor Kidney Transplantation, this term only 4. MeSH descriptor Liver Transplantation, this term only 5. MeSH descriptor Lung Transplantation explode all trees 6. MeSH descriptor Pancreas Transplantation, this term only 7. (solid next organ next transplant*):ti,ab,kw in Clinical Trials 8. kidney next transplant* in Clinical Trials 9. lung next transplant* in Clinical Trials 10. heart next transplant* in Clinical Trials 11. liver next transplant* in Clinical Trials 12. pancreas next transplant* in Clinical Trials 13. (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12) 14. MeSH descriptor Tuberculosis explode all trees 15. (tuberculosis):ti,ab,kw or (tuberculoses):ti,ab,kw in Clinical Trials 16. exp Antitubercular Agents/ 17. (14 OR 15 or 16) 18. (13 AND 17)
MEDLINE	<ol style="list-style-type: none"> 1. organ transplantation/ 2. exp heart transplantation/ 3. kidney transplantation/ 4. liver transplantation/ 5. exp lung transplantation/ 6. pancreas transplantation/ 7. or/1-6 8. exp Tuberculosis/ 9. (tuberculosis or tuberculoses).tw. 10. exp Antitubercular Agents/ 11. or/8-10 12. and/7,11
EMBASE	<ol style="list-style-type: none"> 1. organ transplantation/ 2. heart transplantation/ 3. kidney transplantation/ 4. liver transplantation/ 5. lung transplantation/ 6. pancreas transplantation/ 7. or/1-6 8. exp tuberculosis/ 9. (tuberculosis or tuberculoses).tw. 10. exp tuberculostatic agent/ 11. or/8-10 12. and/7,11

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	<i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	<i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	<i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	<i>Unclear:</i> Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	<i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	<i>Unclear:</i> Insufficient information to permit judgement

(Continued)

<p>Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors</p>	<p><i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken</p> <hr/> <p><i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding</p> <hr/> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data</p>	<p><i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods</p> <hr/> <p><i>High risk of bias:</i> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation</p> <hr/> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Selective reporting Reporting bias due to selective outcome reporting</p>	<p><i>Low risk of bias:</i> The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)</p>

(Continued)

	<p><i>High risk of bias:</i> Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Other bias Bias due to problems not covered elsewhere in the table</p>	<p><i>Low risk of bias:</i> The study appears to be free of other sources of bias.</p> <p><i>High risk of bias:</i> Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem</p> <p><i>Unclear:</i> Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias</p>

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: BA, IT
2. Study selection: BA, AA
3. Extract data from studies: BA, AA
4. Enter data into RevMan: BA
5. Carry out the analysis: BA, IT
6. Interpret the analysis: BA, IT
7. Draft the final review: BA, MB, AB
8. Disagreement resolution: IT
9. Update the review: BA, AA, AB

DECLARATIONS OF INTEREST

None known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Subgroup analysis could not be performed according to the plan presented in the protocol for this review. We had planned to include organ transplant group, but all studies were conducted in kidney transplant patients.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibiotic Prophylaxis [adverse effects; *methods]; Antitubercular Agents [adverse effects; *therapeutic use]; Chemical and Drug Induced Liver Injury [etiology]; Hepatitis B [complications]; Hepatitis C [complications]; Immunosuppression [adverse effects]; Isoniazid [adverse effects; *therapeutic use]; Kidney Transplantation [*adverse effects]; Tuberculosis [*prevention & control]

MeSH check words

Humans