TREATMENT FAILURE IN TUBERCULOSIS

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Short title: Treatment failure in tuberculosis.
ABSTRACT:

Treatment of latent Tuberculosis (TB) infection, with 3 months of Rifampicin/Isoniazid, is a major part of TB preventive programmes. The effectiveness of treatment of Latent TB infection can only be assessed by rates of subsequent breakdown and there are few outcome data for this combination.

Aim of the study was to estimate the failure rate following treatment for the latent TB infection.

We undertook a questionnaire survey of all parents of children under 16 years who completed treatment for latent TB infection at Leicester Royal Infirmary from 1997-2003. Cases of treatment failure were identified by: Reviewing all re-referrals to the clinic, identifying children developing TB disease while on treatment and postal questionnaire to all patients discharged.

Of the eligible 400 children, 344 (86%) replied. 3 children who had latent TB infection subsequently developed TB disease over the time period. Of those 3 patients, 1 developed Chest X Ray signs at the end of treatment and 2 presented with symptoms within 2 years of completing treatment. Overall, treatment failure rate was 0.87% (0.3-2.5) or 2.2 cases per 1000 patient years.

In conclusion rates of TB breakdown after treatment for latent TB infection with 3 months Rifampicin/Isoniazid are acceptably low.

Key words: Latent TB infection, treatment failure
After many years of decline, rates of tuberculosis (TB) in the United Kingdom have remained static and even increased. One of the difficulties in the control of the spread of TB is that, once infected the disease may remain dormant for many years. Strategies for prevention of TB consist firstly of identification and treatment of TB disease and secondly contact tracing and treatment of early disease and latent infection. Treatment of latent TB infection is designed to reduce the burden of future TB and this is particularly appropriate for the young who have a higher risk of progression of disease.

There is data on the effectiveness of treatment of TB disease in adults and it is assumed that treatment of children is probably similar although specific data is scarce. Standard guidelines are available for the management of the TB disease. There is less data on treatment of latent infections. In the UK, standard treatment for latent TB infection is a 3-month course of rifampicin and isoniazid. There is data on safety of this regime but not on efficacy. The purpose of the present study was to estimate the failure rate following treatment of latent infection.

METHODS

Population
The study population was taken from the Leicester TB clinic. All children on anti TB treatment in the geographical area up to 16 years of age are seen in the TB clinic. The population is relatively stable and this makes the sample essentially population based.

Data collection
All children who completed treatment for latent TB infection at Leicester Royal Infirmary (LRI) from January 1997 - December 2003 were included. The list of
children was obtained from the clinic database along with details of age, gender, BCG status, country of origin, source of referral and the relationship to any known index case. Cases of treatment failure were identified by 3 methods 1. Review of all referrals to the clinic. 2. Identifying all children upgraded from latent infection to disease while on treatment and 3. Postal questionnaire to all patients discharged after completion of treatment. The questionnaire was initially piloted on 20 children attending the clinic to assess understandability. All cases who had a second course of treatment were categorised by questionnaire and notes review either as having had further exposure to TB or as treatment failure. There was a repeat mailing for non-responders after one month and remaining non-responders were contacted by telephone after 2 months.

The Questionnaire (Appendix 1) covered whether the child had had TB diagnosed since discharge and also asked about present symptoms which might represent undiagnosed TB i.e., fever, cough, weight loss, night sweats or shortness of breath for more than 3 weeks. Responders with positive symptoms were offered a review appointment and repeat chest X-ray.

**Diagnostic pathway**

The Referrals to the TB clinic came either from GPs because of symptoms, referrals from school screening or referrals from the TB contact tracing service. Children with symptoms were assessed and investigated for the presence of TB as appropriate. For asymptomatic contacts the TB nurses assessed the proximity of the contact to the index case and decided on the need for screening by a standard protocol. In the
presence of significant contact, defined as 6-8 hours per week in the close proximity of the house, work or school environment, all children less than 5 years were referred to our clinic. Children above 5 years of age were initially screened and referred to the children’s TB clinic if the Heaf test was positive (2-4) regardless of previous BCG vaccination. Screening for TB was performed in the clinic using a chest radiograph and Mantoux test (Evans Medical). One tuberculin unit (with prior BCG) or 10 TU (no previous BCG) was administered intradermally on the left forearm and the test was read 48-72 hours later. Induration of 5 mm or more was treated as a positive response. This assessment for latent TB infection in this population has been shown to be more restrictive than current BTS guidelines but with little increase in risk for those not treated.  

Asymptomatic Mantoux positive patients with a normal chest radiograph were treated as having a latent TB infection with a 3 month course of rifampicin and isoniazid (10mg/kg/day and 5 mg/kg/day respectively rounded up to a convenient dose). Children were routinely reviewed in the clinic at 1 month, and again at the end of treatment with additional appointments if clinically warranted. In addition all patients were monitored in the community by the TB nursing service. On successful completion of a course of treatment, patients were discharged from the clinic.

**RESULTS**

400 children (228 male, 172 female) were treated for latent TB infection. The response rate was 50% after the first questionnaire, 65% after repeat mailing and 85% after telephone contact. Eighty six percent (344/400) responded and there was no
difference between responders and non-responders for the base line characteristics except for the increased age of the non-responders.

The demographic characteristics of the children are given in Table 1. The majority of the children were born in UK, had BCG vaccination and were referred following contact with a TB case.

In total, 3 children, subsequently developed TB disease over the time period. Of the 3 patients, 1 developed CXR signs at the end of treatment and in retrospect was non-compliant with treatment. The treatment course was extended and the patient upgraded to a diagnosis of primary TB. The other 2 were referred back to the paediatric TB clinic with symptoms within 2 years of completing treatment where concordance with treatment was felt to have been good. In total, 3 children (0.87%) (0.3-2.5) had treatment failure. This equates with 2.2 cases per 1000 patient years.(Table 2).

Twenty children had persistent symptoms in response to questionnaire. They were contacted by telephone after 2 months. 11 children who still had symptoms were clinically assessed and X-rayed, but none found to have TB. There were 12 children referred back to the clinic with a new contact with TB. None was found to have evidence of TB disease but this group is difficult to assess for presence of a newly acquired infection.

Complications in the present study were uncommon. One child had drug sensitisation. This child was the only child receiving pyrazinamide (the source case had Isoniazid
resistant TB) and the drug had to be substituted after 3 weeks because of a skin reaction.

**DISCUSSION**

This study has demonstrated a failure rate for LTBI treatment of 0.87% (2.2/1000 patient years). The confidence interval is wide given the small number of treatment failures.

The response rate to our questionnaire was high and as the study was population based, the results of this study are probably generalisable to other populations. The characteristics of the non-responders were very similar to the responders except for the higher mean age. This presumably reflects the fact that adolescents and young adults are a more mobile population and more likely to have left the parental home. As this age group has a higher breakdown rate of TB it is possible that the failure rate has been underestimated.

The questionnaire was simple and was pre-tested for understandability. It also included questions about current symptoms and all patients who responded positively were reviewed in the clinic. In the event, no unrecognised TB was diagnosed by this route.

It is difficult to be precise about what the risk of progression from LTBI to TB disease in this group would be if they had not been treated. They certainly represent a high-risk group, in that the majority had had contact with infectious TB (88%) and most of the school age children had a positive Heaf test (grade 2 or more) prior to referral. A
negative Mantoux test (1 tuberculin unit) was used to try to reduce the known false positive effect of BCG before treatment was initiated. The estimated lifetime risk of disease progression for a newly infected young child is 10% with roughly half of the risk occurring in the first 2 years after infection. This risk decreases with age to about 1% at aged 20. The mean age of our group was 8 years and 82% were followed for more than 2 years.

Most of the evidence for effectiveness of LTBI treatment has been with isoniazid monotherapy. This was reviewed by Ferebee in 1970. The populations recruited for these studies were varied and some included children with primary TB as, at the time of enrolment, uncomplicated primary TB was not routinely treated. The difficult diagnostic distinction between primary and latent TB persists and several studies have demonstrated that a chest X-ray has relatively low sensitivity in diagnosing enlarged hilar and mediastinal lymph nodes compared to CT scan. However, in the subgroup most similar to this study (namely; under 15 year olds who were household contacts of tuberculosis and were tuberculin reactors or convertors with normal chest X-ray, followed for up to 10 years) the rate of subsequent pulmonary or extrapulmonary TB was 16.7/1000 patients untreated and 5.7/1000 post treatment compared with our figure of 0.87% (8.7/1000). Methodological differences however, make comparisons difficult. In a small double blinded study of isoniazid versus placebo in young adult contacts of TB, the rates of TB over 7 years for placebo and isoniazid treatment was 9.4% and 0.8% respectively. Overall protection given by isoniazid monotherapy for these and similar studies varied from 70-95% and the failure rates on treatment are broadly in agreement with our results.
A recent meta-analysis, in adults, has compared 3-month dual Isoniazid/Rifampicin therapy against 6-12 month isoniazid monotherapy\textsuperscript{16}. The overall results showed a treatment failure rate of 4.2\% and 4.1\% respectively. While this overall result supports the efficacy of combination treatment, the individual studies varied considerably in methodology and patient characteristics (e.g. HIV status and reason for TB testing) and none was specifically paediatric.

Alternative combinations of drugs have been used for LTBI treatment but have been less than satisfactory. Studies in adults using the Rifampicin/Pyrazinamide combination for 2 months have concluded that the risk of side effects is high\textsuperscript{17}. Only one of our patients received this combination and reacted to the pyrazinamide component. The dosage of drugs used in this study was within the recommended therapeutic range (5mg/kg Isoniazid, 10mg/kg Rifampicin rounded up to the nearest convenient dosage) but there is recent evidence that this may give variable but generally low serum levels of Isoniazid in children\textsuperscript{18}. The significance of this finding is not clear for efficacy of treatment but may mean that higher doses of Isoniazid monotherapy for LTBI would increase cure rates.

The present data shows that 3 month dual therapy with Isoniazid/Rifampicin has acceptably low failure rates and low side effects in this group of patients. Compliance with medication seemed to be high as monitored in clinic and by the TB nursing service but this was not assessed directly. Likewise the potential economic savings of the reduced time of treatment monitoring compared to Isoniazid monotherapy have not been estimated.
REFERENCES


TABLE 1
Demographic characters.

<table>
<thead>
<tr>
<th>Variables</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>228 (57%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>323 (81%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>53 (13%)</td>
</tr>
<tr>
<td>BCG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country of origin</td>
<td>UK</td>
<td>296 (74%)</td>
</tr>
<tr>
<td>Referral category</td>
<td>Contact</td>
<td>351 (88%)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td>7 (2%)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>42 (10%)</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Number of children who were send questionnaire</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>Number responded to questionnaire</td>
<td>344(86%)</td>
<td></td>
</tr>
<tr>
<td>Mean follow up time from completion of treatment</td>
<td>4.02 years</td>
<td></td>
</tr>
<tr>
<td>Repeat referral following new TB contact</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Upgraded during treatment</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Re referral no new contact</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Identified from questionnaire</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Overall failure (rate) (CI) of responders</td>
<td>3 (0.87%) (0.3-2.5)</td>
<td></td>
</tr>
<tr>
<td>Rate of failure per 1000 years (CI)</td>
<td>2.2 (0.7-6.4)</td>
<td></td>
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</table>
Dear Parent / Guardian,

Your child __________ was treated at the LRI on ______

1. Since discharge on __ has your child had any further problems with TB?
   YES □   NO □

If yes which hospital was your child treated in?

Approximate date treatment started:

Approximate date treatment finished:

2. Do you have any of the following TB symptoms now? (Please circle)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td>Fever for more than 3 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough for more than 3 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss for more than 3 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night sweats for more than 3 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath for more than 3 weeks</td>
<td></td>
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</tbody>
</table>

Please give your present home/mobile telephone number in case we need to clarify any of the above details.