

## **INTRODUCTION**

Mycobacterium Tuberculosis (TB) is a bacterium that is spread by a person inhaling the bacteria via aerosol droplets during coughing or sneezing by an individual with infectious TB (NICE 2006). Over the past century the United Kingdom (UK) has made significant progress in combating TB. This has been achieved through improved healthcare and better preventative measures. The epidemiology of TB is changing and it is now identified as a new threat that needs concerted action to deal with it (Department of Health 2004).

An important component of TB control in a country with a low prevalence rate of TB such as the UK, is to identify and treat persons with latent TB infection and therefore prevent the development of active disease (O'Brien 2003). Patient concordance with this treatment is essential as non-compliance may lead to an increase in drug resistance especially to Rifampicin (O'Brien 2003). One of the major barriers to concordance with treatment, as identified by O'Brien (2003), is the requirement of a well person to take the medication over a long period of time with marginal personal benefit. Many studies and surveys indicate that non adherence to latent tuberculosis treatment is considerable. In the United States non-adherence to self administered tuberculosis medication varies from 82% in hard to reach groups to 11% in the general population (McDonnell, Turner and Weaver 2001).

The British National Formulary (BNF 2010) and the National Institute for Clinical Excellence (NICE 2006) recommends two treatment regimens for latent TB infection with either six months of Isoniazid or a shorter three month regimen using a combined treatment with Isoniazid and Rifampicin dependent on age or HIV status.

Traditionally most patients received six months of Isoniazid but there is now a trend to use the shorter 3 month regimen guided by clinician and patient preference (Rennie et al 2007). Research from outside the UK has demonstrated that shorter treatment regimens for latent tuberculosis have significantly improved medication concordance rates. (Spyridis et al 2007, McNeill et al 2003, Lobato et al 2005, Menzies et al 2004 and Lardizabal et al 2006).

## **AIMS AND AUDIT OBJECTIVES**

The aim of the project was to determine whether concordance with TB treatment is affected by the length of the regimen in patients with latent TB infection in the UK.

Audit objectives were to:

1. Determine the completion rates for the treatment of latent tuberculosis infection over a 3 year period.
2. Compare treatment completion rates between the 6 month and 3 month regimens
3. Establish the prevalence of side effects in the 3 and 6 month treatment regimen.
4. Identify whether demographic factors have an impact on treatment completion.

## **AUDIT STANDARDS**

A retrospective clinical audit was conducted to address the aims and objectives.

1. All patients commenced on treatment for latent TB infection should complete their prescribed course of medication with a 100% desired performance level with the exceptions of death or life threatening side effects.
2. All patients identified as suitable for latent TB treatment would be commenced on either Isoniazid monotherapy or a combined treatment of Rifampicin and Isoniazid.

## **SAMPLE**

Clinical records which included patient's records and computerised data were searched to identify patients who met the following criteria.

1. Patients with clinically identified latent TB infection between 1<sup>st</sup> January 2006 and 31<sup>st</sup> December 2008
2. Patients commenced on either a monotherapy of Isoniazid or combined treatment of Rifampicin and Isoniazid between 1<sup>st</sup> January 2006 and 31<sup>st</sup> December 2008

A total of 57 patients fulfilled the criteria for inclusion in the audit.

## **RESULTS**

### **Characteristics of the sample**

Ages ranged from 16-80 years with a mean age of 33 years. Thirty eight patients (66.7%) were born outside of UK. In non-UK born patients, ethnic origin was split into TB notification format which identified the largest patient population as Black African 33.3% (19), Pakistani 19.3% (11), Chinese 3.5% (2) and other 12.3% (7).

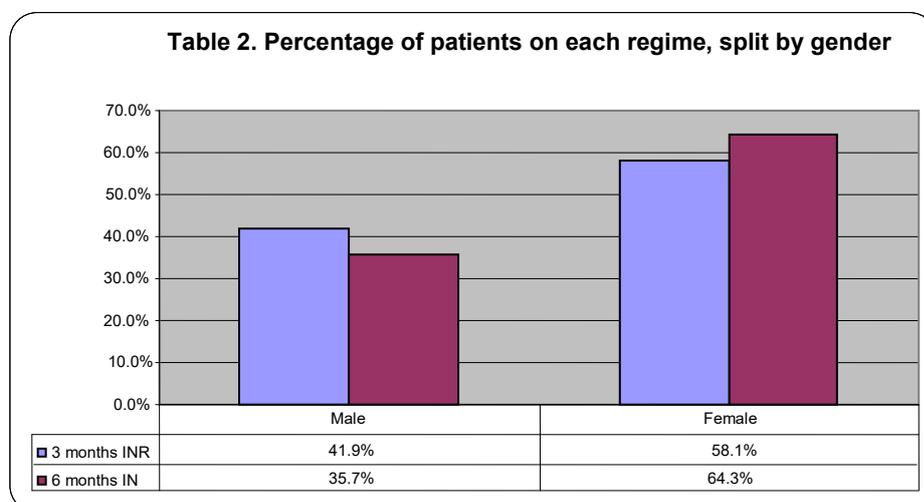
Referral to the service during the three year period was split into six main areas with the highest number of patients being asylum seekers referred by local GP practice (Table 1).

Table 1. Patient numbers by method of referral to the TB service

Source of referral	No. of patients (%)
Asylum seekers identified through local GP practice	21 (36.8%)
Identification through contact tracing	12 (21.1%)
Identification through pre-treatment assessment (for drugs such as anti-TNF therapy)	9 (15.8%)
Identification through new immigrant screening via port health forms	7 (12.3%)
Occupational health pre-screening	6 (10.5%)

### Characteristics of treatment and treatment regimen

Forty three patients (75.4%) were commenced on the combined treatment of Rifampicin and Isoniazid for 3 months compared with 24.6% (14) patients who were commenced on Isoniazid monotherapy for 6 months (Table 2). Patient records were examined to identify whether the regimen was changed during treatment from the 3 to 6 month or 6 to 3 month regimen. Thirty five (81.4%) patients on the 3 month regimen remained unchanged during treatment, while the rest of patients later changed treatment to the 6 month regimen. It was reported that this change was due to side effects, pregnancy or drug interaction. None of the patients on the 6 month regimen changed to the three month regimen during treatment (Table 3).



## Side effects of treatment

Side effects or adverse reactions were identified from the patient's notes and measured using known side effects identified in the BNF (2010). Side effects of treatment were noted with both regimens, with a higher proportion of patients in the three month regimen (46.5%) reporting side effects than on the six month treatment regimen (28.5%). The most commonly reported side effects were nausea (10%), urticaria (10%) and rash (10%).

When the presence of side effects was examined by age, the younger age group had fewer side effects (16 – 24 yrs) of which 26% reported one or more side effects. This percentage rose to 50% in the 25 – 34; 35 – 44 and 45 – 54 year age groups and but interestingly dropped to 44% in the over 55 year old group. There were no differences in the frequency of side effects based on ethnicity.

## Treatment completion and concordance

Overall treatment completion (both regimens) was seen in 40 patients (70.2%). Four (7%) patients did not complete their treatment either out of choice (2), abnormal liver function (1) or not known (1) while 13 were lost to follow up or their treatment completion was unknown (22.8%). The results for each treatment regimen are shown in table 2.

Table 3. Completion rates and reasons for non-completion

	3 month regimen (n= 43)	6 month regimen (n=14)
Completed treatment	67.4% (29)	78.6% (11)
Did not complete	7.0% (3)	7.1%% (1)
Lost to follow up	25.6% (11)	14.3% (2)
Switched regimen	18.6% (8)	0.0%(0)

Review of socio-demographic data revealed more men (78%) than women (65%) completed their treatment. Treatment completion was higher in UK born patients (79%) compared with non UK born patients (66%). A greater number of non UK born patients were lost to follow up 29% (11) compared to UK born patients 11% (2).

Table 4: Age group and completion of treatment:

Age	Completed Treatment	Frequency	Percentage
16 - 34	Yes	28	49.1%
	No	2	3.6%
	Not know (lost to follow up, side effects)	12	21.0%
35 – 55+	Yes	12	21.0%
	No	2	3.6%
	Not known	1	1.7%

## **DISCUSSION**

The aim of this retrospective audit was to determine whether concordance with TB treatment is affected by the length of the regimen in patients with latent TB and the relationship between side effects or demographics and treatment regimen used.

The results of this audit indicate that changing from a monotherapy six month treatment regimen to a combined therapy three month treatment regimen has not improved treatment concordance. In this study, treatment completion rates were higher in the single therapy treatment group (78.6%) when compared with the combined therapy treatment group (67.4%). This contradicts findings from outside the UK where shorter treatment regimens with combined therapy reported improved treatment completion rates than the longer Isoniazid therapy treatment regimen (Spyridis et al 2007, McNeill et al 2003, Lobato et al 2005, Menzies et al 2004 and Lardizabal et al 2006).

The reason for this difference is unclear. Current guidelines within the United States recommend monotherapy using either Isoniazid for 6 or 9 months or Rifampicin for 4 months. A combination of Rifampicin and Pyrazinamide is no longer recommended for the treatment of latent TB because of the high rate of hepatotoxicity (Centre for Disease Control 2005). This is not consistent with current recommendations in the UK (NICE 2011).

Seemingly poorer treatment completion in the three-month combined therapy group may have been influenced by loss to follow up in this group and may be partly explained by differences in the prevalence of side effects. In this study, 46.5% of patients (20) in the 3-month combined regimen group experienced side effects compared with 28.5% (4) in the 6 month single therapy group. Although only 3 patients reported side effects as the reason for stopping their treatment, it is

reasonable to assume that the majority of those lost to follow up were lost due to patient decisions to stop treatment or issues out of their control.

It appeared that the identified non completion rate in both groups was approximately 7% but 8 patients did change from the 3 month to 6 month regimen which helped maintain the overall completion rate of 70.2%.

The audit identified that 22.8% of the total study population were lost to follow up patients who could not be accounted for, whether they fully completed their treatment, partially completed their treatment and if not for what reason and whether there were any adverse events in this group. Lost to Follow up rates vary in some studies such as Lardizabal et al (2006) who reported a rate of 34.7% in their 9 month regimen but only 12.6% in their 4 month regimen, while Kwara et al (2008) reported a 35.6% lost to follow up rate with the use of a 9 month treatment regimen. The results of this are therefore consistent with existing literature in this respect

The main concern in this study appears to be the large number of lost to follow up patients. We were unaware whether these patients completed their medication and the possibility of partial treatment raises the issue of multi-drug resistant TB (MDR-TB).

When considering whether the patient was UK born or not, 29% of the non UK study population were more likely to be lost to follow up compared to only 11% of the UK population. The two main groups identified as lost to follow up were Black African 26% and 'Other' 57% which included patients from the European and Asian continents. Age revealed that the younger age group were more likely to be lost to follow up, with 38% of the 16-24 year age group, 23% of the 25-34 year age group and 25% of the 35-44 year age group. None of the older age group were lost to follow up and appeared to be a more stable study population.

Dalal et al (2008, pg 101) reported similar data in a lost to follow up specific single centre study with 1 in 6 patients lost to follow up. This appears to be a problem in TB treatment and can have direct consequences when it comes to preventing MDR-TB and the difficulties this would present. Treatment completion in this study is encouraging but to eliminate TB further attention needs to be focused on completion rates to prevent active infection.

## **STUDY LIMITATIONS**

The results of this study may not be applicable to other social groups or populations. A considerable number of patients were lost to follow-up were potential side effects and completion of treatment are not entirely clear. The 6 month group was significantly underrepresented in this study.

## **KEY FINDINGS**

1. Treatment completion is higher in the six month group although the total number of patients in this group was lower than the 3 month group
2. The three month group experienced more side effects
3. Younger patients experienced more side effects and were more likely to be lost to follow up
4. There was a substantial lost to follow up rate
5. Further studies are required to identify specific demographics of patients lost to follow up and measures to reduce their numbers.

## **CONCLUSION**

Overall, the completion of treatment for latent TB infection has not been affected by the introduction of the 3 month treatment regimen in this population with concordance actually better in the 6 month regimen. The study has highlighted the concern of lost to follow patients. The study demonstrated that patients under 35 years of age who were non UK born i.e. belonged to either the Black African or Pakistani population groups were more likely to be lost to follow up. This group needs to be targeted specifically when treating patients with latent TB infection.

## **CONFLICT OF INTEREST**

Non

## **REFERENCES**

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