BTS recommendations for assessing risk, and for managing *M.tuberculosis* infection and disease in patients due to start anti-TNF-alpha treatment

British Thoracic Society Standards of Care Committee

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FINAL VERSION
SOCC APPROVED

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Introduction

In view of the increased risk of TB reactivation with anti-TNF alpha treatment, various professional groups have sought the advice of the Joint Tuberculosis Committee of the British Thoracic Society. The objectives of these guidelines are to quantify these risks, and to give advice on the treatment of TB disease and infection, in patients being assessed for anti-TNF alpha treatment. The risks and benefits of treatment for latent TB infection, in those unsuitable for tuberculin skin testing, are also covered. These guidelines are intended to inform respiratory physicians, gastroenterologists, rheumatologists and dermatologists, together with specialist nurses in those disciplines.

Abstracted bullet points

* In patients receiving anti-TNF-alpha treatment there is an increased risk of clinical tuberculosis (TB) developing.

* Patients should have a clinical examination, their history of any prior TB treatment checked, a chest X-ray and if appropriate a tuberculin test (see text). Any patient with an abnormal chest X-ray or previous history of TB or TB treatment should be referred for assessment by a specialist with an interest in TB. (D)

* Patients with an abnormal chest X-ray and/or symptoms raising a suspicion of TB should be thoroughly investigated to exclude active disease. (D)

* Any patient with active TB, either pulmonary or non-pulmonary, should receive standard chemotherapy (A).

* Patients with active TB should receive a minimum of 2 months full chemotherapy directed by a specialist in TB, before starting anti-TNF-alpha treatment. (D)

* Patients with an abnormal chest X-ray consistent with past TB, or a history of
4.

prior extra-pulmonary TB but who have received previous adequate treatment, should be monitored regularly. (D)

* Active TB should be excluded by appropriate investigations in patients with an abnormal chest X-ray or a history of prior pulmonary or extra-pulmonary TB not previously adequately treated, should have active TB excluded. Chemoprophylaxis should be given before commencing anti-TNF-alpha treatment. (A)

* For patients with a normal chest X-ray who are not on immunosuppressive therapy a tuberculin test is helpful in management: an algorithm is supplied. (D)

* For those with a normal chest X-ray who are on immunosuppressive therapy a tuberculin test will not be helpful and need not be undertaken. An individual risk-assessment should be made (Tables 3-4); if the annual risk of TB is greater than the risk of drug-induced hepatitis, then chemoprophylaxis should be given (C). If the risk of hepatitis is the greater the patient should be monitored regularly with suggestive symptoms promptly investigated to permit early diagnosis of active disease. An algorithm is supplied (C). In general, Black-African patients aged over 15, and all South Asians born outside the UK, should be considered for chemoprophylaxis with isoniazid for 6 months (6H).

* Close co-operation between clinicians prescribing anti-TNF therapy and specialists in the management of TB is strongly recommended. (D)
ALGORITHM FOR MANAGEMENT OF TB IN PATIENTS SCHEDULED FOR anti-TNF-alpha TREATMENT

Notes for algorithm

Mantoux equivalence for Heaf tests will be 0-5mm induration = Heaf grade 0-1: 6-14mm Heaf 2: 15mm or greater Heaf 3-4

Where the Tuberculin test is unreliable this should not be performed and patients stratified for TB risk (see Tables 3-4)

Give chemoprophylaxis if TB risk (Tables 3-4) greater than chemoprophylaxis (Table 5). In general, Black-African aged over 15, and all South-Asians born outside the UK should be considered for chemoprophylaxis with isoniazid for 6 months (6H).

If chemoprophylaxis risk is greater than TB risk repeat chest X-ray within 3 months of starting anti-TNF treatment/investigate if required.

All patients on TB treatment or prophylaxis should have this managed by thoracic or infectious disease physician. Clinical awareness of the possibility of TB should be maintained throughout anti-TNF treatment and for a period of up to 6 months after cessation of anti-TNF treatment.
1. Search methodology

1.1. Structure of the recommendations

The format follows that used for other BTS guidelines. At the start there is a summary of the abstracted bullet points from each section. Following that there is an algorithm summarizing the management of patients due to start anti-TNF-alpha treatment. The recommendations use the revised SIGN grading system available on [http://www.sign.ac.uk/guidelines/fulltext/50/section6.html](http://www.sign.ac.uk/guidelines/fulltext/50/section6.html) (Table 1). The primary source literature has been individually graded for its methodology (where appropriate) and the grading is given alongside the reference using the revised SIGN levels of evidence (Table 2).

1.2. Methodology for the generation of the recommendations

The initial systematic literature search (Pubmed, EMBASE) was carried out by one of the committee (LPO), using tuberculosis and biologics 1997-2003 and chemoprophylaxis for TB and hepatitis 1966-2002 as search criteria. A paper-based exploration of the relevant literature was pursued from this core dataset.
Only English language literature, including clinical trials and all well-formulated clinical case series were identified. Isolated case reports and abstracts were excluded.

After the data appraisal, the guideline was initially drafted by LPO, and then discussed by the whole group, the evidence debated, and several re-draftings took place. The draft was based where possible on the published evidence, but this was combined with clinical expertise where required. The resulting draft was a blend of published evidence and clinical expertise. The manuscript was then placed on the BTS website for consultation by the membership, it was also reviewed by the British Societies for Rheumatology and Gastroenterology. Following this, further amendments took place, and the document was reviewed by the Joint Tuberculosis and Standards of Care Committees of the BTS. After final approval from this Committee, the Guidelines were submitted for peer review prior to publication.
1.3 Conflict of interest

All members of the Guideline Committee were asked to submit a written record of possible conflicts of interest to the Standards of Care Committee of the BTS. None were recorded.
2. Introduction

2.1 The need for recommendations

The increase in active tuberculosis associated with anti-TNF therapy\(^{1,9-11}\) has led to a requirement to screen for active and latent tuberculosis in patients before anti-TNF-alpha treatment is given. This screening, suggested by manufacturers to include tuberculin skin testing, is further complicated by the fact that many patients, up to 79% in the infliximab study\(^1\), were receiving immunosuppressive therapy such as maintenance prednisolone, azathioprine, 6-mercaptopurine, methotrexate, cyclophosphamide, ciclosporine, tacrolimus or mycophenolate mofetil which would interfere with the accuracy of tuberculin skin testing\(^2,3\). The product licence for infliximab states that the product should be used in conjunction with methotrexate or other immunosuppressants, and in practice the other anti-TNF agents would also normally be used with other immunosuppressants. Chemoprophylaxis, or preventive therapy, for TB itself carries a small risk, with drug induced hepatitis being the main issue, increasing
with age and occasionally fatal. It is also important to exclude active TB disease before chemoprophylaxis is given, particularly as single agent chemoprophylaxis given when active disease is present could lead to the development of drug resistance. These problems have led to many requests for advice in this area.

2.2 Background Epidemiology

Infliximab, a murine human chimera monoclonal antibody against TNF-alpha, is approved in the USA and Europe for the treatment of rheumatoid arthritis and Crohn’s disease\(^5\) and ankylosing spondylitis. Etanercept is a fusion protein that binds free TNF-alpha using the soluble portion of tumour necrosis factor receptor (TNFR2) coupled with an Fc moiety\(^6\), and is also used in the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthropathy and juvenile idiopathic arthritis. Adalimumab, a recombinant fully humanized monoclonal antibody against TNF, became licensed for the treatment of rheumatoid arthritis in September 2003\(^7\).
Post-marketing surveillance in the USA and beyond to the end of May 2001, showed 70 cases of TB associated with infliximab use, a much lower number of cases being reported with etanercept. Cases of TB are also described with Adalimumab. The majority of the cases of TB in patients given infliximab occurred within 3 cycles of treatment, with a median of 12 weeks after commencing treatment. The frequency of tuberculosis was much higher than other opportunistic infections reported with the drug, and was higher than reported background rates. Over 50% of reported TB cases associated with anti-TNF alpha therapy are extra-pulmonary. The number of cases of TB reported to the US Food and Drugs Administration had risen to 117 by December 2001, giving a recalculated TB prevalence of 41/100000 in infliximab/etanercept treated USA patients with rheumatoid arthritis, 9/100000 in USA patients with Crohn’s disease, and 224/100000 in all non-USA patients with rheumatoid arthritis or Crohn’s disease. The number of TB cases now reported has reached 242 (Keane J personal communication 2004), the curve of which has leveled off due to either...
improved TB risk assessment, tuberculin testing and isoniazid prophylaxis, and/or reporting fatigue.

The estimated prevalence of tuberculosis in rheumatoid arthritis patients in the USA is 6.2/100000 (95% CI 1.6-34)\textsuperscript{11}, with that in patients on infliximab being originally 24.4/100000\textsuperscript{1}, an approximate four-fold increase. In a second part of the prevalence study\textsuperscript{11}, TB incidence among infliximab-treated patients was 52.5/100000 (95% CI 14.3-134.4), an approximate 8-fold increase, but based on only a very small number of TB cases. Overall the subcommittee believes the average risk factor for anti-TNF-alpha treatment to be a five-fold increase {D}. 

\textsuperscript{1}The last three numbers are footnotes. 

\textsuperscript{11}The last two numbers are references.
3.1 Risks of tuberculosis

Tuberculosis incidence varies markedly within the United Kingdom (UK) according to a number of factors\textsuperscript{12,13}. These are age, ethnic group, and for those non-UK born, the length of time since first entry. Where possible data on the current annual risk of tuberculosis have been updated from those derived from continuous enhanced surveillance (Table 3).

3.2 Risks of drug-induced hepatitis from TB chemoprophylaxis

A database search (Medline and Embase) was carried out on the reported hepatotoxicity of antituberculosis chemoprophylaxis from 1966-2002 in adults. Children were excluded because they have a very low rate of drug reactions, and studies in HIV-positive individuals excluded because such individuals have a higher than normal drug reaction profile\textsuperscript{14}. The hepatitis rates for various regimens were derived from these data (Table 5).
Only hepatitis sufficient to stop treatment (symptomatic) or Grade 3 alanine transferase (ALT 5-20 times normal) or grade 4 (ALT > 20 times normal) hepatitis is reported here. Co-infection with HIV, hepatitis B or C contraindicate the use of anti-TNF therapies according to manufacturers, so this guidance does not apply to patients with these co-infections.
4. Recommendations

4.1 Assessment before anti-TNF treatment

Patients should have a clinical examination, their history of any prior TB treatment checked, a chest X-ray and if appropriate a tuberculin test (Sections 4.4 and 4.5). Any patient with an abnormal chest X-ray or previous history of TB or TB treatment should be referred to a specialist with an interest in TB, either a thoracic or infectious disease physician. Close co-operation between clinicians prescribing anti-TNF therapy and specialists in the management of TB is strongly recommended. (D)

4.2 Active TB found before anti-TNF alpha treatment

Patients with chest X-ray abnormalities (e.g. infiltrates, cavitation, pleural effusion or mediastinal lymphadenopathy) and/or symptoms raising a suspicion of tuberculosis should be thoroughly investigated to exclude active disease. This should include sputum microscopy and culture for acid-fast bacilli, and if indicated bronchoscopy and washings, and biopsy and culture of pleura and/or
mediastinum. Extra-pulmonary sites may require material to be obtained by aspiration for culture or biopsy for culture and histology. (D)

Any person with active TB, either pulmonary or non-pulmonary, should receive standard chemotherapy\(^\text{15}\) (A). Anti-TNF-alpha treatment should not be commenced a) for at least two months after antituberculosis treatment with full compliance has begun, supervised by a thoracic physician or infectious disease specialist, and b) until the drug susceptibility profile of the organism in those with positive cultures is known, as a minimum. (D) Ideally it would be preferable to delay anti-TNF treatment until completion of a full course of antituberculosis treatment. (D)

4.3 Inactive tuberculosis found before anti-TNF-alpha treatment

a) Previous adequate treatment

Patients with an abnormal chest X-ray consistent with past tuberculosis, or a history of prior extra-pulmonary TB but who have received previous adequate
treatment, as judged by a thoracic or infectious disease physician, can start anti-TNF-alpha treatment but should be monitored clinically every 3 months, with a chest X-ray and sputum cultures if respiratory symptoms develop. (D) The onset of new respiratory symptoms, particularly within 3 months of commencing anti-TNF treatment, should be investigated promptly (D).

b) Previous inadequate treatment

Patients with an abnormal chest X-ray or a history of prior pulmonary or extrapulmonary TB not previously adequately treated, should have active tuberculosis excluded by appropriate investigations (see 4.2) under the care of a thoracic or infectious disease physician. In such individuals even when active disease has been excluded, the annual risk of tuberculosis (reactivation) is much higher than the general population rate\(^\text{16}\), so the risk-benefit analysis strongly favours chemoprophylaxis (section 4.6)(A).

Ideally, chemoprophylaxis for TB for patients in this category should be completed before starting anti-TNF treatment. If the clinician is concerned
about the potential 6 month delay in starting such treatment, discussion should be
held with the patient and the clinician supervising chemoprophylaxis, about using
a shorter (but potentially more toxic) chemoprophylaxis regimen (see 4.6).

4.4 Patients with normal chest X-rays and assessable by skin tuberculin test

For patients with a normal chest X-ray who are not on immunosuppressive
therapy, a tuberculin test is helpful in management. The tuberculin test needs to be
interpreted in the light of the BCG history. In those without a BCG history, Heaf
grades 0-1 (Mantoux 1:10000 0-5mm) are negative, but Heaf grades 2-4
(Mantoux 1:10000 6mm or greater) are positive, and should lead to a risk
assessment. In those with a prior BCG history, confirmed by scar or adequate
documentation, Heaf 0-2 grades (Mantoux 1:10000 0-14mm) need no
action, but Heaf grades 3-4 (Mantoux 1:10000 15mm or greater) may represent
either latent infection or BCG effect, so require a risk assessment: an algorithm is
supplied (Figure 1).

4.5 Patients with normal chest X-rays and not assessable by skin tuberculin
test
The majority of potential recipients of anti-TNF-alpha medication will have a normal chest X-ray and will have been on immunosuppressive therapy thus hindering the interpretation of tuberculin testing. In these individuals an individual risk-benefit calculation will be needed. The estimated annual risk of tuberculosis disease (Table 3) should be multiplied by a factor of 5 to give an annual risk on anti-TNF treatment, based on the current reported rates of TB in association with such therapies.

If the calculated annual risk on anti-TNF treatment is higher than the risk of hepatitis, then the risk/benefit favours chemoprophylaxis; if lower the risk/benefit calculation favours observation and investigation of symptoms. Table 4 gives worked examples. In general, Black-Africans aged over 15, and all South Asians born outside the UK should be considered for chemoprophylaxis with isoniazid for 6 months (6H).

4.6 Chemoprophylaxis
There are 2 potential chemoprophylaxis regimens: isoniazid for 6 months (6H), rifampicin plus isoniazid for 3 months (3RH). Rifampicin and pyrazinamide for 2 months (2RZ) was a regimen used in the USA\textsuperscript{17}, but had a very high hepatitis rate (Table 5) with a number of fatalities reported\textsuperscript{18,19}. Accordingly the choice of regimen is between 6H which has a lower hepatitis rate, and 3RH which may have advantages in terms of shorter duration and thus possibly better adherence (Table 5), and also less risk of drug resistance developing if active disease is present (A). The decision on the chemoprophylaxis regimen should be made by the thoracic or infectious disease physician following informed discussion with both the patient and the referring clinician. (D)

In contrast to patients falling into category 4.3b (above), chemoprophylaxis for patients with normal chest X-rays not assessable by tuberculin skin tests can start concurrently with anti-TNF treatment. If the chemoprophylaxis regimen contains rifampicin, any maintenance dose of prednisolone should be doubled for
its duration, and note made of interaction with other immunosuppressive agents e.g. tacrolimus and ciclosporine treatment. (D)

It should be noted that no chemoprophylaxis regimen is wholly effective, protective efficacies being 60% for 6H27 and 50% for 3RH24. If patients who have had chemoprophylaxis develop symptoms suggestive of clinical TB they should be promptly and appropriately investigated. (D)

4.7 Management of clinical TB developing during anti-TNF-alpha treatment

If a patient develops active tuberculosis while on anti-TNF-alpha treatment, they should receive full antituberculosis chemotherapy15. (A) In these circumstances, which are different from TB disease diagnosed before anti-TNF-alpha treatment has started, the anti-TNF-alpha treatment can be continued if clinically indicated, because the patient would otherwise be prevented from receiving the continued clinical benefit to their underlying disease, and may have a flare up or major clinical deterioration (D). Although there are no good data in this area, it is known that HIV-positive individuals with reduced CD4 counts and clinical TB, who are
even more immunosuppressed than those on anti-TNF-alpha treatment, respond
just as well to TB treatment as in those who are HIV-negative\textsuperscript{14}.

\textbf{Suggested Guidelines review date: Summer 2008}
5. References, Tables and suggested Audit Criteria

5.1 References


2. Joint Committee on Vaccination and Immunisation. Tuberculin testing in Chapter 32: Vaccination and Immunisation. 1996. HMSO.


8. HUMIRA prescribing information: Issues December 2002, Abbott Laboratories, North Chicago, IL 60064, USA.


5.2 Tables

TABLE 1   REVISED SIGN GRADING SYSTEM – GRADES OF RECOMMENDATION

A  At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or
A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.

B  A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+.

C  A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2+.

D  Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+. 
<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.</td>
</tr>
<tr>
<td>1+</td>
<td>Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.</td>
</tr>
<tr>
<td>1-</td>
<td>Meta analyses, systematic reviews of RCTs or RCTs with a high risk of bias.</td>
</tr>
<tr>
<td>2+++</td>
<td>High quality systematic reviews of case-control or cohort or studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.</td>
</tr>
<tr>
<td>2+</td>
<td>Well conducted case control or cohort studies with a very risk of confounding, bias, or chance and a moderate probability that the relationship is causal.</td>
</tr>
<tr>
<td>2-</td>
<td>Case control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal.</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytical studies e.g. case reports, case series.</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
TABLE 3 ANNUAL RISK OF TUBERCULOSIS DISEASE/100000 IN ENGLAND AND WALES

(A) Effect of Age (to the nearest whole number)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>White</th>
<th>Black-African</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>15-34</td>
<td>2</td>
<td>314</td>
</tr>
<tr>
<td>35-54</td>
<td>4</td>
<td>168</td>
</tr>
<tr>
<td>55-74</td>
<td>7</td>
<td>204</td>
</tr>
<tr>
<td>&gt;75</td>
<td>11</td>
<td>not available</td>
</tr>
</tbody>
</table>

(B) Effect of Place of birth/Duration of residence in England and Wales

<table>
<thead>
<tr>
<th>Age</th>
<th>Place of birth</th>
<th>Years after first entry</th>
<th>All patient Rate</th>
<th>ISC* ethnic Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>UK</td>
<td></td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Abroad</td>
<td></td>
<td>31</td>
<td>88</td>
</tr>
<tr>
<td>15 and over</td>
<td>UK</td>
<td></td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>15-34</td>
<td>Abroad</td>
<td>0-4</td>
<td>180</td>
<td>540</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 years and over</td>
<td>53</td>
<td>87</td>
</tr>
<tr>
<td>35 and over</td>
<td>Abroad</td>
<td>0-4</td>
<td>146</td>
<td>593</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 years and over</td>
<td>39</td>
<td>108</td>
</tr>
</tbody>
</table>
TB data from case reports to Enhanced TB Surveillance 2000 Health Protection Agency
*ISC= Indian Subcontinent

How to use (see also Table 4)
If white UK born use data from Table 1A
If Indian subcontinent (ISC) use Table 1B
If Black-African use Table 1A (similar data to Table 1B not yet available)
If either white non-UK born or other ethnic group use All patient rate Table 1B

If in doubt or in special circumstances consult local thoracic physician
TABLE 4  Sample Calculations based on Tables 3A and 3B

The weighted average risk for prophylaxis with isoniazid (6H) is 278/100000 which is used for these calculations. That for rifampicin/isoniazid (3RH is higher at 1766/100000 but this regimen may need to be considered if a shorter duration of chemoprophylaxis is needed on clinical grounds (see 4.6)

<table>
<thead>
<tr>
<th>Case Type</th>
<th>Annual risk of TB disease/100000</th>
<th>TB risk adjusted x5 for anti-TNF effect</th>
<th>Risks of prophylaxis /100000 (Table 5)</th>
<th>Risk/benefit conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>White 55-74 UK born</td>
<td>7</td>
<td>35</td>
<td>278</td>
<td>Observation</td>
</tr>
<tr>
<td>Indian sub Continent &gt;35 In UK 3 years</td>
<td>593</td>
<td>2965</td>
<td>278</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>Black-African 35-54</td>
<td>168</td>
<td>840</td>
<td>278</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>Other ethnic 35 or over In UK &gt;5 years</td>
<td>39</td>
<td>195</td>
<td>278</td>
<td>Observation</td>
</tr>
<tr>
<td>Reference</td>
<td>N=</td>
<td>Hepatitis/100000*</td>
<td>% Completion</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------</td>
<td>----</td>
<td>------------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Regimen Isoniazid 6H</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>6965</td>
<td>480</td>
<td>78</td>
<td>65% protective efficacy (1 death from 6H)</td>
</tr>
<tr>
<td>21</td>
<td>282</td>
<td>1000</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>
| 22        | 11141 | 100 | - | Female OR 3.3 (0.87-12.45)  
White OR 2.6 (0.75-8.95)  
Increase with age Chi² 5.22 |
| 23        | 427  | 1170 | - | |
| **Weighted average** 18815 | 278 | | |
| **Regimen Rifampicin/isoniazid 3RH** | | | | |
| 24        | 170  | 1766 | - | 50% protective efficacy in silicosis |
| **Regimen Rifampicin/pyrazinamide 2RZ** | | | | |
| 25        | 148  | 9459 | 57 | Female OR 4.1 (1.2-14.3)  
Recent tuberculin conversion OR 14.3 (1.8-115) |
| 21        | 307  | 7700 | 61 | Age>35 OR 12.2 (1.49-100.3)  
OR 8.46 x isoniazid (1.9-76.5) |
| 26        | 114  | 5300 | 67.5 | |
| **Weighted average** 569 | 6648 | | |

H=isoniazid   R=Rifampin   Z=Pyrazinamide   * Symptomatic or grade 3/4 hepatitis.
5.3 Suggested Audit criteria

History of previous TB checked  Y/N

Chest X-ray within 3 months of starting anti-TNF alpha treatment?  Y/N

Chest X-ray normal?  Y/N

If abnormal referred to TB specialist?  Y/N

Tuberculin skin test possible pre-treatment?  Y/N

If No – referred for risk stratification?  Y/N

If skin test performed – positive?  Y/N

If risk stratification performed – given treatment for latent TB infection?  Y/N
Figure 1.

Symptoms suggest active TB/ previous history of TB/ Abnormal CXR?

- Yes
  - Investigations confirm active TB?
    - Yes
      - 6 months treatment start TNF-alpha after at least 2 months
      - Monitor and reassess if symptoms develop
    - No
      - Exclued activity
    - No
      - Active Disease
  - No
    - On Immunosuppressant treatment?
      - Yes
        - Had BCG?
          - Yes
            - Tuberculin Test
            - Heaf 0-2
            - Mantoux < 15mm
            - No action
          - No
            - Tuberculin Test
            - Heaf 0-1
            - Mantoux < 5mm
            - Stratify for TB Risk (see tables 3 & 4)
        - No
          - Tuberculin Test
          - Heaf 0-1
          - Mantoux < 5mm
          - No action
      - No
        - Tuberculin Test
  - Yes
  - Adequate Chemotherapy in past?
    - Yes
      - Monitor and reassess if symptoms develop
    - No
      - Exclude activity
      - No
      - Active Disease

Tuberculin Test Unreliable