5. Clinical Management

The cornerstone of an effective TB control programme is prompt and accurate diagnosis, effective treatment and identification and appropriate management of contacts. The management of contacts is dealt with in chapter 8. This requires a multidisciplinary team approach involving clinicians, public health staff, the laboratory and pharmacists.

5.1 Diagnosis

General practitioners and all other medical staff should maintain a high index of suspicion in relation to TB. CDC recommends that patients in the following situations should be evaluated for TB: [215]

- Any patient with a cough of ≥ 3 weeks duration with at least one additional symptom, including fever, night sweats, weight loss or haemoptysis
- Any patient at high risk of TB[ϒ] with an unexplained illness, including respiratory symptoms of ≥ 3 weeks duration
- Any patient with HIV infection and unexplained cough and fever
- Any patient at high risk of TB with a diagnosis of community-acquired pneumonia who has not improved after seven days of treatment and
- Any patient at high risk for TB with incidental findings on chest X-ray suggestive of TB even if symptoms are minimal or absent.

Recommendation:

All persons with an otherwise unexplained productive cough lasting three or more weeks with at least one additional symptom, including fever, night sweats, weight loss, or haemoptysis should be evaluated for tuberculosis.[25] This will include clinical, radiological and bacteriological examinations.

Recommendation:

All cases of suspected active TB should be referred to a TB clinic and have a clinical assessment at the next available clinic.[216] If immediate evaluation is required, consult with the clinical team regarding the need for more urgent clinical assessment. The management of suspect TB cases can be undertaken in collaboration with the clinical team (respiratory or infectious diseases) who will advise on sputa collection and the clinical management (including commencement of therapy, if the sputa are positive for AFB), until the next clinic appointment.

Where pulmonary TB is suspected, a clinical evaluation including examination should be undertaken preferably by a respiratory physician or infectious disease consultant with appropriate training in the management and treatment of TB. The evaluation should include an interview conducted in the patient's primary language with the assistance of qualified medical interpreters, if necessary.

Diagnostic investigations should include chest X-ray, sputum smear microscopy and culture. All persons with chest X-ray findings suggestive of TB should have sputum specimens submitted for microbiological examination.[25] Culture for *M. tuberculosis* complex (MTC) is considered the gold standard for diagnosis. Specimens may need to be obtained by sputum induction, broncheoalveolar lavage (BAL) or gastric lavage particularly in children[77] (see chapter 4 on laboratory diagnosis).

[ϒ] **Patients with one of the following characteristics: recent exposure to an infectious case; history of a positive test result for *mycobacterum tuberculosis* (MTB) infection; HIV infection; injection or non-injection drug use; foreign birth and immigration in ≤ 5 years from high endemic region (TB rate ≥ 40/100,000 per annum); residents and employees of high-risk congregate settings; membership of a medically underserved, low-income population; or a medical risk factor for TB e.g. diabetes, immunocompromised patients.**

All patients (adults, adolescents and children who are capable of producing sputum) suspected of having pulmonary TB should ideally have three sputum specimens obtained for microscopic examination. When possible at least one early morning specimen should be obtained.[25] The recommendations in chapter 4 on laboratory diagnosis should be implemented in this regard.

A sputum smear positive patient has a minimum of one sputum specimen positive for AFB by microscopy.[24] The diagnosis of sputum smear negative pulmonary TB should be based on the following criteria:

- At least three negative sputum smears (including at least one early morning specimen)
- Chest X-ray findings consistent with TB and
- Lack of response to a trial of broad-spectrum antimicrobial agents.[25]

As fluoroquinolones are active against *M. tuberculosis* complex and thus cause transient improvement in persons with TB, they should be avoided. For such patients, if facilities for culture are available, sputum cultures should be obtained. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.[25]

An assessment of the likelihood of drug resistance based on history of prior treatment, exposure to a possible source case having drug-resistant organisms and the community prevalence of drug resistance should be obtained from all patients.

In an era of increasing drug resistance every effort should be made to obtain bacteriological diagnosis in order to obtain drug susceptibility data. This is also critical for obtaining molecular typing data essential for contact tracing and TB control programmes. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin should be performed promptly.[25]

Where extrapulmonary TB is suspected, specimens from the suspected sites of involvement should be obtained for microscopy, culture and histology.[25] The NICE guidelines suggest various site-specific investigations for the diagnosis of extrapulmonary TB (see table 5.1).[26]

CDC now recommends that NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established and for whom the test result would alter case management or TB control activities such as contact tracing.[158] All those wishing to undertake NAAT on suspected cases of pulmonary TB should seek advice from the local consultant microbiologist (see chapter 4 on laboratory diagnosis of TB).

Table 5.1: Suggested site-specific investigations in the diagnosis of extrapulmonary TB[26]

Site	Imaging	Biopsy	Culture
Lymph node		Node	Node or aspirate
Bone/joint	Plain X-ray and CT scan MRI	Site of disease	Biopsy or para-spinal abscess Site or joint fluid
Gastrointestinal	Ultrasound CT abdomen	Omentum Bowel	Biopsy Ascites
Genitourinary	Intravenous urography Ultrasound	Site of disease	Early morning urine Site of disease Endometrial curettings
Disseminated	CT thorax Ultrasound abdomen	Lung Liver Bone marrow	Bronchial wash Liver Bone marrow Blood
CNS	CT scan MRI	Tuberculoma	Cerebrospinal fluid (CSF)
Skin		Site of disease	Site of disease
Pericardium	Echocardiogram/MRI	Pericardium	Pericardial fluid
Cold/liver abscess	Ultrasound	Site of disease	Site of disease

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Children

The diagnosis of TB in children can be difficult because of non-specific symptoms and infrequent isolation of the organism. WHO recommends that diagnosis should be based on a careful history, clinical examination, and relevant investigations including tuberculin skin test, chest X-ray and sputum smear microscopy.[217] Caution should be used when interpreting chest X-ray changes in children (and particularly so in very young children), as changes are less specific than in adults. The approach to be taken should be discussed with the consultant radiologist.

The diagnosis of intrathoracic (i.e. pulmonary, pleural and mediastinal or hilar lymph node) TB in symptomatic children with negative sputum smears should be based on the finding of chest X-ray abnormalities consistent with TB and either a history of exposure to an infectious case or evidence of TB infection (positive TST). For such patients, if facilities for culture are available sputum specimens should be obtained (by expectoration, induced sputum or gastric washings) for culture (chapter 4).[25]

5.2 Supervision of TB Treatment

Recommendation:

Treatment of TB should be directed by a consultant respiratory physician/consultant in infectious diseases with appropriate training in the management and treatment of TB.

Drug-resistant TB

Treatment of patients with drug-resistant TB is complicated. The drugs used are toxic and expensive and the outcome is not always successful in inexperienced hands. Treatment should always be directed by a consultant respiratory physician/consultant in infectious disease with appropriate training in the

management and treatment of TB. Treatment should be in line with the International Standards for TB Care (ISTC) (appendix 8) and should be given for at least 18 months.[25]

Children
Children with TB disease should be treated and managed by a consultant paediatrician with appropriate training in the management and treatment of TB in children. In areas where a consultant paediatrician with appropriate training is not available, the committee recommends joint supervision of such patients by a respiratory physician/consultant in infectious disease and the diagnosing consultant paediatrician.

5.3 Role of Public Health Staff in Clinical Management

Under the Infectious Disease Regulations 2003, all TB cases (confirmed or presumed) are statutorily notifiable to the medical officer of health (MOH).[21] The role of public health doctors includes the identification of contacts of TB cases and arrangement of appropriate investigations (symptom questionnaire, tuberculin testing, chest X-ray, sputum examination) and chemoprophylaxis. Contacts in receipt of chemoprophylaxis are reviewed on a monthly basis or more frequently if indicated.

When a TB case occurs in a healthcare setting, effective contact tracing requires liaison between public health services, hospital infection prevention and control and occupational health services. Coordination of contact tracing is most appropriately led by hospital infection prevention and control (vis. consultant microbiologist) in those healthcare settings where this is in place. This will include the initial alerting of public health and occupational health services. In all other healthcare settings, coordination should be undertaken by the public health service.

Compliance with treatment is one of the most important determinants of treatment outcome and a significant aspect of the work of public health staff (doctors and nurses) is to develop strategies to improve compliance. Public health doctors also work with treating clinicians, public health nursing staff and pharmacists in the management of patients who may require DOT. They also have a role in the ongoing education and training of other health professionals, both within the hospital setting and within the community.

Recommendation:

There should be active case management with a dedicated case manager or health care professional who liaises with and follows the patient during the entire treatment course to monitor and enhance adherence.

Combined clinics attended by both respiratory physicians and public health staff have operated as models of good practice throughout the country for the diagnosis and treatment of TB and the evaluation of contacts. Ideally all TB clinics should be based on this model. There is a need for the physician, public health staff and the pharmacist to have a strong working relationship for the successful management and treatment of TB.

Recommendation:

More widespread establishment of combined clinics attended by both respiratory physicians and public health doctors for the diagnosis and treatment of TB (and LTBI) and the evaluation of contacts is recommended. Such clinics should be appropriately staffed with medical, nursing, pharmacy, administrative staff and medically qualified interpreters and should be integrated with the hospital system.

Role of the pharmacist in the management of TB

It is recommended that a pharmacist is a member of the clinical team and attends the combined clinics where they have an important role to play in: 1) dispensing of TB medications to patients and maintaining dispensing records; 2) providing appropriate written and verbal information to patients to enable them to understand and comply with their medication; 3) promoting and monitoring patient compliance with their medication regime; 4) screening for potential drug interactions, monitoring adverse drug reactions and advising on their management, particularly for patients with MDR-TB and HIV-TB co-infection; 5) maintaining links with community and hospital pharmacy services where appropriate and 6) participating in research and audit.

The committee also encourages the development and maintenance of regional collaborative TB committees throughout the country. These multidisciplinary committees can review regional epidemiology and local strategies for the prevention and control of TB.

5.4 Treatment of Tuberculosis

Effective chemotherapy taken over an adequate period of time is the guiding principle of treatment for all forms of TB (pulmonary and extrapulmonary). The objective of anti-TB therapy is to achieve a lifetime cure of the disease while preventing drug resistance.[30]

All patients (including those with HIV infection) who have not been treated previously for TB should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability.[25]

Recommendation:

Isoniazid (H) and rifampicin (R), with pyrazinamide (Z) and ethambutol (E) for the initial two months (intensive phase), followed by isoniazid and rifampicin for a further four months (continuation phase) is recommended in patients with sensitive strains of tuberculosis and where there are no contraindications.

As susceptibility results are not available at the start of treatment, regimens can be adjusted as these results become available. Under certain circumstances the continuation phase may be extended beyond four months.

Because of the difficulties with increased pill burden/medication volume and difficulty in monitoring for E toxicity an initial three-drug (HRZ) regimen is often acceptable in children, who generally have a low bacillary burden. For children for whom there are specific concerns regarding resistance or the presence of CNS involvement, and for adolescents, an initial four-drug regimen should be used.

Recommendation:

Six months of chemotherapy is usually adequate for drug-susceptible pulmonary TB (table 5.2). However, clinical trials have shown that selected patients have a higher rate of relapse with a six month regimen and may benefit from longer treatment. [77;128;218;219] Therapy should be extended to nine months in the following cases:

- Patients who have drug-susceptible pulmonary TB with initial cavitation on chest X-ray and whose sputum cultures remain positive after the intensive phase i.e. the first two months of therapy
- Other patients who are still culture positive at two months regardless of chest X-ray results
- Patients whose treatment regimen did not include pyrazinamide in the intensive phase or whose organism is resistant to pyrazinamide
- Patients being treated with once-weekly isoniazid and rifampicin whose sputum culture remains positive after the two month intensive phase of treatment.[77]

Recommendation:

Follow-up sputum specimens for smear and culture should be obtained monthly in patients with drug-susceptible pulmonary disease. Requests for more frequent testing should only be undertaken following discussion between the treating clinician and consultant microbiologist. For patients with isoniazid- and rifampicin-susceptible TB there is no need to examine sputum monthly once culture conversion is documented (i.e. two negative cultures taken at least two to four weeks apart).[77] It is recommended that identification and sensitivities are repeated in cases who are still culture positive at ≥ two months.

Bacteriological monitoring i.e. culture at the end of treatment in confirmed cases is strictly recommended to assess precisely that the patient has been cured. A negative sputum culture at the end of treatment is the only conclusive evidence that the patient has been cured.[77]

EuroTB classifies treatment failures as patients who have culture or sputum microscopy remaining positive or becoming positive again at the fifth month or later during treatment.[10] Patients who fail treatment should be assessed by a consultant respiratory/infectious disease physician with appropriate training in the management and treatment of TB for possible drug resistance and have therapy modified accordingly.

In cases of extrapulmonary TB, the same regimens should apply, though in certain circumstances, treatment may need to be more prolonged e.g. TB meningitis, miliary/disseminated disease. In such cases, a longer course of therapy is suggested, especially in children, in whom 2 months of at least three drugs in the initial phase and 10 months of two or more drugs in the continuation phase are recommended, assuming that the initial isolate is fully drug sensitive.[30] In patients with extrapulmonary TB and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and may be misleading.[25]

M. bovis is invariably resistant to pyrazinamide and a three-drug nine month regimen is indicated (RHE_2 + RH_7).

Patients should be assessed monthly during the initiation phase and one to two monthly during the continuation phase of therapy, depending on their level of compliance, likelihood of treatment-related adverse events etc. (see appendix 5: TB therapy audit form).

A written record of clinical symptoms and examination, all medications given, adverse reactions, adherence to treatment and bacteriological response should be maintained on all patients.[25] The assessment should include an interview conducted in the patient's primary language with the assistance of qualified medical interpreters, if necessary.

The prompt recognition and appropriate management of adverse drug reactions is an essential part of the treatment programme and clinicians, nurses and pharmacists responsible for drug therapy need to be well acquainted with these reactions (table 5.2). Toxicity and hypersensitivity reactions require that the offending drug(s) be discontinued. However, this should be accompanied by careful evaluation of the reaction and identification of the offending drug(s) to avoid unnecessary cessation of a first-line drug.[30]

If a DOT programme is employed, a three-times-weekly regimen may be used if acceptable to the patient (table 5.2). Agents such as streptomycin, amikacin, quinolones, etc. should only be used under the supervision of a consultant respiratory physician or consultant in infectious disease with appropriate training in the management and treatment of TB. Advice on potential drug interactions and adverse effects should be sought from the pharmacist on the clinical team.

Table 5.2. Dosages for primary medications used in the treatment of tuberculosis

Drug *Mode of action*	**Route of administration**	**Daily dose [max]**	**3 Times a week dose [max]**	**2 Times a week dose [max]**	**Major adverse reactions***
Isoniazid *Bactericidal*	Oral/ Intramuscular	Children: 5-10mg/kg[1] Adults: 5mg/kg [300mg]	Children: 20mg/kg Adults: 10mg/kg (range 8-12mg/kg) [900mg]	Children: 20mg/kg Adults: 15mg/kg (range 13-17mg/kg) [900mg]	Hepatic enzyme elevations, hepatitis, rash, peripheral neuropathy, CNS effects, increased phenytoin levels, possible interaction with disulfiram
Rifampicin *Bactericidal*	Oral/ Intravenous	Children: 10-20mg/kg[2] Adults: 600mg (range 8-12mg/kg) [600mg]	Children: 10-20mg/kg Adults: 600mg (range 8-12mg/kg) [600mg]	Children: 10-20mg/kg Adults: 600mg (range 8-12mg/kg) [600mg]	Hepatic enzyme elevations, hepatitis, rash, fever, thrombocytopaenia, influenza-like syndrome, reduced levels of many drugs (including methadone, warfarin, hormonal forms of contraception, oral hypoglycaemic agents, theophylline, dapsone, ketoconazole, PIs, and NNRTIs)
Pyrazinamide *Bacteriostatic*	Oral	Children: 25mg/kg (range 20-30mg/kg) Adults: 25mg/kg (range 20-30mg/kg) [2.0g for adults and children	Children: 35mg/kg (range 30-40mg/kg) Adults: 35mg/kg (range 30-40mg/kg) [3.0g for adults and children	Children: 50mg/kg (range 40-60mg/kg) Adults: 50mg/kg (range 40-60mg/kg) [3.5g for adults and children	Gastrointestinal (GI) upset, hepatotoxicity, hyperuricaemia, gout (rarely), arthalgias, rash
Ethambutol *Bacteriostatic*	Oral	Children: 20mg/kg (range 15-25mg/kg) [1.5g] Adults: 15-25mg/kg [2.0g]	Children: 30mg/kg (range 25-35mg/kg) Adults: 30mg/kg (range 25-35mg/kg) [2.8g]	Children: 40-50mg/kg [2.5g] Adults: 45mg/kg (range 40-50mg/kg) [3.6g]	Decreased red-green colour discrimination, decreased visual acuity, skin rash
Streptomycin *Bactericidal*	Intramuscular/ Intravenous	Children: 15-30mg/kg Adults: 15mg/kg [1.0g]	Children: 15mg/kg Adults: 15mg/kg [1.0g]	Children: 15mg/kg Adults: 15mg/kg [1.0g]	Auditory toxicity, renal toxicity, hypokalaemia, hypomagnesaemia

*All toxicities are not listed here. Full prescribing information should be checked in the package insert or pharmacology texts.

Table 5.2. Contd.

Drug	Recommended regular monitoring	Comments
Isoniazid	- Monthly clinical evaluation - Liver function tests[3]	- Vitamin B_6 (pyridoxine) 10mg/day may decrease peripheral neuritis and CNS effects and should be used in patients who are abusing alcohol, pregnant, breastfeeding infants on isoniazid, malnourished, or who have HIV infection, cancer, chronic renal or liver disease, diabetes, or pre-existing peripheral neuropathy - Aluminium-containing antacids reduce absorption - Drug interactions with several agents
Rifampicin	- Monthly clinical evaluation - Complete blood cell count including platelets and liver function tests as indicated[3]	- Orange discolouration may occur in contact lenses and body secretions such as tears and urine - Patients receiving methadone will need their methadone dosage increased, by an average of 50%, to avoid opioid withdrawal - Interaction with many drugs leads to decreased levels of the co-administered drug - May make glucose control more difficult in people with diabetes. - Contraindicated for patients taking most PIs and NNRTIs - Patients should be advised to use barrier contraceptives while on rifampicin
Pyrazinamide	- Monthly clinical evaluation - Liver function tests as indicated[3]	- May complicate management of diabetes mellitus - Hyperuricaemia can be used as indicator of compliance - Treat increased uric acid only if symptomatic - Allopurinol increases level of pyrazinamide by inhibiting xanthine oxidase resulting in failure of allopurinol to lower serum uric acid
Ethambutol	- Monthly clinical evaluation - Check colour vision and visual acuity monthly	- Optic neuritis may be unilateral; check each eye separately. If possible avoid in children too young to undergo vision testing. - If patient develops visual complaints, refer for prompt ophthalmologic evaluation. May need to discontinue ethambutol while awaiting evaluation.
Streptomycin	- Monthly clinical evaluation - Audiometry, renal function, electrolytes, including magnesium	- Ultrasound and warm compresses to injection site may reduce pain and induration

[1]World Health Organization (WHO), International Union against TB and Lung Disease (IUATLD), and British Thoracic Society (BTS) recommend 5mg/kg in children; Centers for Disease Control and Prevention (CDC), American Thoracic Society (ATS), Infectious Disease Society of America (IDSA) and the American Academy of Paediatrics (AAP) recommend 10-20mg/kg
[2]WHO, IUATLD, and BTS recommend 10mg/kg in children; CDC/ATS and the AAP recommend 10-20mg/kg
[3]Liver function tests are indicated if baseline is abnormal or patient has risk factors for toxicity

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Recommendation:

To enhance compliance and to minimise potential problems from the development of drug resistance, it is strongly recommended that only combination tablets should be used.

Syrup/tablet dosage should be rounded up or down to facilitate the prescription of easily given volumes/tablets. All cases of TB placed on the above regimens for active disease should be notified to the local public health physicians. In addition, the committee recommends routine audit of both inpatient and outpatient care of TB.

Care should be taken in writing prescriptions so that rifadin (contains rifampicin only) is not confused with rifinah (contains rifampicin and isoniazid) and rifater (contains rifampicin, isoniazid and pyrazinamide).

Pyridoxine

Pyridoxine is often used in conjunction with anti-TB drugs to prevent side effects in the peripheral and central nervous systems. It is recommended that pyridoxine 10mg daily (20mg daily may be used if 10mg tablets are not available) should be prescribed for:

- All adults, including pregnant women
- Children who have poor nutrition and therefore are at risk of pyridoxine deficiency
- Children who develop paraesthesia
- Breastfeeding infants on isoniazid
- A fully breastfed infant if the mother is on isoniazid, regardless of whether the infant is on anti-TB treatment
- In particular, those with pre-existing peripheral neuropathy diabetes, chronic renal or liver disease, cancer, alcoholism, malnutrition, other immunosuppressive disorders or HIV.[52 77]

As there are no side effects to low dose pyridoxine, many centres routinely prescribe it to prevent the development of neuropathy.[30] However, it is not routinely prescribed in children except in the situations mentioned above.

Monitoring

Baseline LFTs and a complete blood count including platelets and biochemistry panel (including creatinine) should be obtained from all patients prior to commencing TB therapy. Monthly follow-up blood testing is not necessary if the baseline is normal unless a patient develops symptoms consistent with adverse drug reactions.

Other relevant laboratory tests should be obtained according to the medications used and side-effects present (see table 5.2). For example, renal function and hearing may be affected by the aminoglycosides and capreomycin; uric acid levels are affected by pyrazinamide. (Note: an increase in uric acid is not an indication to discontinue pyrazinamide as long as the patient remains asymptomatic). Thyroid function tests should be performed for patients on para-aminosalicylic acid or ethionamide.

Management of adverse reactions: hepatotoxicity

Several anti-TB medications cause hepatoxicity (see table 5.2). In addition, concomitant use of TB medications increases the risk of developing drug-induced liver damage. Despite these risks, the benefits of TB treatment to the individual far outweigh the risks. Concomitant use of other known hepatotoxic agents should be avoided if possible during anti-TB treatment especially in patients with underlying liver disease. **A consultant with expertise in TB should always be consulted when treating a patient with active TB disease with documented hepatotoxicity.**

Follow-up

In most cases of TB, it is desirable to review the patient at six months after completing treatment as relapses, should they occur, tend to present within this time. Unless there is a specific cause for concern the patient may be discharged at this time.

Anti-TB regimens in pregnancy

The risk of untreated TB to a pregnant woman and her foetus is far greater than the risk of the toxic effects from the drugs used in its treatment.[220] In a pregnant woman who has active TB disease as verified by a positive *M. tuberculosis* culture or who is highly suspected of having active TB it is essential that prompt effective treatment be administered. Very rarely, following risk assessment by and approval from the treating clinician, treatment for suspected TB may be deferred until the end of the first trimester. This may be done if the pregnant woman is very reluctant to take the treatment and meets all the following criteria:

- Sputum smear negative for AFB
- HIV-negative

- No risk factors for HIV infection
- Has no symptoms of TB i.e. cough, fever, weight loss or night sweats
- Has no cavitation on chest X-ray.[77]

The use of isoniazid, rifampicin and ethambutol have been well studied during pregnancy and their use is safe in this setting.[221] The use of aminoglycosides (streptomycin, amikacin and kanamycin) and the polypeptide capreomycin are contraindicated during pregnancy.[30;77] The effect of pyrazinamide on the foetus is not known. However, if treatment is started after the first trimester, pyrazinamide should be included in the initial treatment regimen for the following women:

- Women who are HIV positive
- Women with behavioural risk factors for HIV infection but decline HIV testing
- Women suspected of having MDR-TB.

Despite the lack of data on pyrazinamide, WHO recommends its use at all stages of pregnancy for all pregnant women.[77]

Standard regimen for pregnant women

The initial treatment regimen in pregnancy should consist of isoniazid, rifampicin and ethambutol unless there are absolute contraindications.[30] Pyridoxine 10mg daily (20mg daily if 10mg tablets are not available) is recommended for pregnant and breastfeeding women (unless the patient is already on a prenatal vitamin supplement that contains the equivalent amount of pyridoxine).

Pregnant women suspected or known to have MDR-TB

Unlike the treatment of drug-susceptible TB, it is not possible to develop standardised protocols for the treatment of known or suspected MDR-TB. As with all drug-resistant TB cases, expert consultation should be sought with a respiratory physician or infectious disease consultant.

Anti-tuberculosis medications in breastfeeding women

The small concentrations of anti-TB drugs in breast milk are not toxic to the nursing newborn. Therefore, breastfeeding should not be discouraged for women who are HIV negative and who are planning to take or who are taking isoniazid or other anti-TB medications. Furthermore, the low concentration of anti-TB medications in breast milk should not be considered effective treatment for disease or for treatment of LTBI in a nursing infant. Women who are HIV positive should not breastfeed because of the risk of HIV transmission to the infant. [77]

5.5 Inpatient or Outpatient Management

Many patients do not require admission to hospital either for investigation or initiation of treatment for TB. However, a minority will be acutely ill and will require admission to hospital. These include:

- Those with severe forms of TB such as: central nervous system (CNS) and meningeal TB, pericardial TB or disseminated or miliary TB
- Haemodynamic instability
- Severe haemoptysis
- Severe debilitation with weight loss, severe cough, high fevers and inability to care for themselves
- Advanced AIDS
- Co-morbid medical conditions that require treatment in hospital.[77]

Other indications for admission include:

- MDR-TB or XDR-TB
- Toxicity from medication
- Poor compliance

- Social reasons e.g. having no fixed abode, alcohol or drug abuse, not ambulatory and needing professional home care e.g. home help
- The need for isolation because of:
    - particularly vulnerable (immunosuppressed or children under five years of age who have not been evaluated for LTBI and window period prophylaxis) household or other contacts or
    - living in a congregate setting such as a nursing home. [77]

Others will require admission to clarify the diagnosis.

On a practical basis, young children will often require hospital admission to complete TB investigations.

Recommendation:

It is recommended that the supraregional TB centre at St. James's Hospital and a number of regional centres should have a small number of non-acute beds available to facilitate the inpatient care of patients who are non-compliant or have drug-resistant TB.

The beds should be on the campus of an acute general hospital and each unit should have adequate recreation and rehabilitation facilities. For patients who require inpatient supervision throughout the course of their treatment, 'stepdown' beds in a non-acute facility may be appropriate when the patient is clinically stable.

5.6 Adherence and Directly Observed Therapy (DOT)

Treatment of TB is very effective. The International Standards for Tuberculosis Care state that any practitioner treating a patient for TB is assuming an important public health responsibility. To fulfil this responsibility, the clinician must not only prescribe an appropriate treatment regimen but must also be capable of assessing the adherence of the patient to the regimen and of addressing poor adherence when it occurs.[25] The responsibility for successful treatment lies with public health in cooperation with the treating physician.[30] However, patients should be involved in their treatment decisions from the onset and the importance of adherence should be emphasised.[26]

In this context, it is essential that patients take their medication as prescribed by the consultant respiratory physician/consultant in infectious disease. Treatment completion is a fundamental principle of TB control. Failure to complete treatment can result in patient relapse, a potential to infect contacts and an increased risk of drug resistance. The most important reason for failure is that patients do not take the prescribed drugs regularly or for long enough.[222] The importance of adherence is therefore central to establishing good cure rates for TB and preventing the emergence of drug resistance. As the patient improves and feels better, compliance may be more problematic.

To foster and assess adherence, a patient-centred approach to administration of drug treatment based on the patient's needs should be developed for all patients. A central element of the patient-centred strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. Supervision and support should be gender-sensitive and age-specific. The measures should be tailored to the individual patient's circumstances.[25] In this regard, the committee recommends the appointment of a key worker/treatment supporter for each patient. TB services should

also provide medically qualified interpreters and patient information in the relevant language. The NICE guidelines recommend the following interventions if a patient defaults from treatment: reminder letters in the appropriate language, patient-centred interview and health education booklet; health education counselling; home visits; patient diary and random urine tests and other monitoring e.g. pill counts.[26]

Directly observed therapy (DOT)

DOT is a way of helping patients to take their medicine for TB. A person receiving DOT will meet with a healthcare worker/key worker everyday or several times a week at an agreed place e.g. the patient's home, the TB clinic or other convenient location. The healthcare worker will observe the patient taking their medication at this place helping to ensure that higher treatment completion rates are achieved. Sometimes someone in their family or a close friend will be able to help in a similar way to the healthcare worker.

Blumberg *et al* have reported completion rates of between 85 and 90% using DOT. These compared with completion rates of 60% after self-administration of therapy.[219] In addition, the use of DOT has also been shown to reduce the rate of drug resistance and relapse when compared to self-administered therapy.[223]

The key worker will be actively involved in the administration of DOT and should actively monitor and ensure compliance. They should also be acceptable and accountable to the patient and to the health system.

However, the availability of DOT is currently limited and needs to be improved in the majority of HSE areas. Where universal provision of DOT is not feasible because of resource limitations, the following circumstances should be given priority:

- Suspected or proven drug-resistant organisms
- Treatment failure
- Documented re-treatment disease
- Injection drug users/homeless persons
- Suspected non-adherence or previous non-adherence
- HIV infection
- Children
- Psychopathology
- Too ill to self administer
- Smear positive for AFB[30;77;224]

Ormerod *et al* have shown that DOT may be selectively used when not all patients are being treated with DOT and at least 90% of patients complete treatment (no culture done at the end of treatment) or are cured (negative culture at the end of treatment).[224]

The establishment of a structured national DOT programme is vital for the effective management and control of TB and in particular, for effective control of TB among foreign-born cases.

Recommendation:

Prioritising the establishment of a structured national DOT programme is recommended for more effective management and control of TB.

This will require close coordination between the secondary care hospitals and the public health service.

Staff supervising DOT should be appropriately trained. The regimen should be determined by the treating physician in conjunction with the patient. In some cases, an intermittent regimen may be appropriate. In others, a daily regimen is more appropriate. See HSE South (Cork and Kerry) DOT referral form in appendix 9.

In addition, procedures for monitoring compliance such as pill counts need to be established early in the treatment of the disease. Blister packs labelled with each day's TB medication will also facilitate compliance. Pharmacists should be involved in monitoring compliance. In order to monitor and improve compliance, the patient should receive their anti-TB medications from the same pharmacy on a monthly basis. Electronic records of each dispensing should be maintained and ongoing liaison between the pharmacist and prescriber is recommended. Medication must be easily accessible for the patient and ideally should be available at the diagnosing clinic/hospital.

A directly observed therapy short-course strategy (DOTS strategy), the internationally recommended approach by WHO to TB control has been successfully implemented in many countries but requires careful institution and monitoring. This comprises five components as follows: (i) political commitment with increased and sustained financing; (ii) case detection through quality-assured bacteriology; (iii) standardised treatment with supervision and patient support; (iv) an effective drug supply and management system; and (v) a monitoring and evaluation system and impact measurement. [5] The committee recommends endorsement of the WHO DOTS strategy at the highest level.

Use of DOT in MDR-TB and XDR-TB

In all cases of MDR-TB and XDR-TB the use of DOT is recommended. A daily regimen is more appropriate.

Use of DOT in children

Three times weekly therapy is not generally recommended for children but twice or thrice weekly administration of rifampicin and isoniazid by DOT can be considered after completion of the initial two month period of treatment in selected circumstances.

5.7 Legislation

Compliance with medication is core to TB control. In practice, a subset of patients are noted who are non-compliant with treatment and are resistant to any intervention in the community. Under Section 38 of the Health Act, 1947 the MOH may order the detention and isolation of an infectious person until that person is no longer a probable source of infection.[225] Section 35 of the Health Act, 1953 amends the 1947 Act, directing that the order must be signed by the MOH and another registered medical practitioner.[226]

This legislation dates back to the 1940s and 1950s (1947 and 1953). It gives the power to detain non-compliant patients but does not give the power to ensure that patients comply with treatment. Personal communication with HSE areas has highlighted a number of enforcement-related issues in recent times primarily with regard to treatment refusal, place of detention and personal rights. This legislation is currently being reviewed by a HSE committee.