DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS

The HIV epidemic has greatly increased the incidence of tuberculosis (TB) and complicated TB diagnosis: smear-negative pulmonary TB and extrapulmonary TB account for 60% of total case load. The aim of this policy is to standardize the diagnosis and management of TB.

A. Diagnosis of TB

1. Patients who require admission and who are coughing productively should have 2 or more sputum specimens sent for AFB smears within 24 hours of admission.
2. Sputum induction using hypertonic saline and ultrasonic nebulization should be performed within 24 hours of admission for all TB suspects with a non-productive cough [See Policy: Sputum collection and ultrasonic sputum induction].
3. Ambulant patients who do not require admission and who have been coughing for >2 weeks should be referred to their nearest Primary Health clinic for sputum smears for AFB, according to national guidelines.

The ‘Cough Warriors’

The ‘Cough Warriors’ are clinical auxiliaries who assist with delivery of TB specimens for AFB to the laboratory and return the results to the patients file.

TB Cultures

The results for all specimens sent for TB culture are filed in the TB Office between the main entrance and the Staff Health clinic.

Note: All TB suspects should be offered testing for HIV infection using the VCT service.

I. Sputum smear-positive pulmonary TB (PTB)

Note: Mark AFB microscopy ONLY on the sputum form

Sputum AFB results should be available in the ward within 48 hours of the sample being sent.

Patients with at least one positive smear should be notified with smear-positive TB (note ‘scanty positive’ result is accepted as positive).

II. Sputum smear-negative PTB

See Annexures 1 and 2 for the WHO algorithms.

Patients can be diagnosed with smear-negative PTB if ALL of the following criteria are met:

1. Cough >2 weeks
2. Two or more sputa smear-negative OR non-productive cough
3. Pulmonary infiltrate compatible with TB present on current CXR (including micronodular OR nodular infiltrates)
4. No clinical response to oral antibiotics after 2 weeks OR intravenous antibiotics after 3 days
5. Pneumocystis pneumonia excluded clinically
6. Decision by a clinician at the level of Senior Medical Officer or above to commit the patient to a full course of antituberculous therapy

Patients meeting all criteria should be notified with smear-negative PTB
Requesting TB culture and sensitivities

TB culture should be requested if:
1. A patient is being re-treated for TB
2. If the patient is diagnosed with smear-negative TB, pleural TB, extrapulmonary TB
3. A patient is sputum smear-positive after 7-11 weeks of TB therapy (failure to convert)
4. A patient is referred for failure to thrive (‘non-responder’) after 2-8 weeks of TB therapy (see definition below)
5. A patient is an MDRTB suspect (see definition below)

Sputum culture has the highest yield - ask for an induced specimen for patients with non-productive cough or prescribe nebulised saline. Pleural aspirate, ascites aspirate, cold abscess aspirate can be inoculated into a myco-F-lytic culture bottle.

Note: Mark AFB microscopy, culture and sensitivity and indication for request (e.g. retreatment case, failure to thrive on TB treatment)

III. Pleural TB

Diagnose pleural TB if:
1. A pleural aspirate returns fluid
2. Fluid clinically has a high protein content (straw colour, 4+ protein on dipstick) OR protein clot forms on standing.
3. Empyema excluded on clinical examination of aspirated fluid (i.e. fluid not cloudy or purulent and pH >5 on dipstick)

If pleural malignancy suspected (age 45 years, blood-stained effusion):
1. Assess smoking history, and other features of malignancy (e.g. breast mass; hard, enlarged lymph nodes; hoarseness; chest pain)
2. Send fluid for cytology (half fluid, half alcohol solution [kept in schedule 6 cupboard])

Note: in equivocal cases send fluid total protein, serum total protein and bacterial culture; pleural biopsy can be subsequently performed.

IV Extrapulmonary TB (EPTB)

EPTB should be diagnosed in patients with constitutional symptoms (fever, weight loss, night sweats, fatigue) by a specialist, CMO, PMO or registrar based on:
1. Mediastinal or intra-abdominal lymphadenopathy
2. Peripheral lymphadenopathy – asymmetric lymphadenopathy with caseating granuloma or giant cells seen on cytology or histology
3. Pericardial effusion >10mm in diameter
4. Ascitic exudates (serum albumin to fluid albumin gradient <11) – send specimen for cytology in alcohol if malignancy suspected

Note:
1. TB arthritis is diagnosed on arthroscopic synovial biopsy; TB spine should be diagnosed on MRI. These cases are managed by the Department of Orthopaedic Surgery
2. TB peritonitis is diagnosed on imaging, with or without laparoscopy. These cases are managed by the Department of General Surgery – contact Dr Islam, Department of Surgery.

V TB meningitis (TBM)

TBM should be diagnosed by a specialist, CMO, PMO or registrar based on CSF analysis showing:
1. Duration of symptoms >5 days
2. Pleiocytosis (usually with lymphocytic predominance)
3. Elevated protein and low glucose (gradient <0.5 calculated using blood glucose or finger prick glucose OR glucose <1.9)
B. Management of TB

TB should be treated according to national guidelines with fixed dosed combination therapy according to weight. Streptomycin should be added for patients receiving retreatment for TB. Doses are calculated according to weight - see below. [Reference: South African Medicines Formulary 7th Edition 2005 page 290-291]

TB pericarditis and miliary TB: Prednisone should be added: 80 mg daily for 7 days, then 60 mg daily for 7 days, then 40 mg daily for 7 days, then 20 mg daily for 7 days, then 10 mg daily 7 days, then 5 mg daily for 7 days

TBM: Dexamethazone intravenously should be added (0.4 mg per kilogram per day for week 1, 0.3 mg per kilogram per day for week 2, 0.2 mg per kilogram per day for week 3, and 0.1 mg per kilogram per day for week 4) and then oral treatment for four weeks, starting at a total of 4 mg per day and decreasing by 1 mg each week. Usual therapy would be 8 mg tds for 7 days, then 6 mg tds for 7 days, then 4 mg tds for 7 days, then 2 mg tds for 7 days, then 2 mg bd for 28 days, decreasing by 1 mg per week.

If oral dexamethazone is not available prednisone or dexamethazone can be substituted, at a starting dose of prednisone 80 mg bid or betamethazone 10 mg bid.

Note: Iron supplementation should not be given to patients with TB unless iron deficiency has been diagnosed using iron studies

Record keeping

The details of all TB suspects should be entered in the TB suspect register, and the final diagnosis documented.

Referral to the TB clinic

Patients referred to the TB clinic should have:
1. Discharge summary (if inpatient)
2. TB referral form (pink)
3. Seven days of TB medication from the pharmacy
4. Counselling from the TB team on how to access TB therapy from the Primary Health Care Clinics
5. A Zulu TB information pamphlet giving details of the District TB control system

First-line antituberculous drugs

<table>
<thead>
<tr>
<th>Drugs dose for weight</th>
<th>Mode of action</th>
<th>Potency</th>
<th>Recommended (mg/kg of body)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>bactericidal</td>
<td>high</td>
<td>5</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>bactericidal</td>
<td>high</td>
<td>10</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>bactericidal</td>
<td>low</td>
<td>25</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>bactericidal</td>
<td>low</td>
<td>15</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>bacteriostatic</td>
<td>low</td>
<td>15</td>
</tr>
</tbody>
</table>

Rifafour e-275 (each tablet contains):

Rifampicin 150 mg
Isoniazid 75 mg
Pyrazinamide 400 mg
Ethambutol 275 mg
Example of recommended treatment dosages,

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-37 kg</td>
<td>2 tablets</td>
</tr>
<tr>
<td>38-54 kg</td>
<td>3 tablets</td>
</tr>
<tr>
<td>55 - 70 kg</td>
<td>4 tablets</td>
</tr>
<tr>
<td>71 kg and over</td>
<td>5 tablets</td>
</tr>
</tbody>
</table>

RIFINAH-150: Patients weighing less than 50 kg: 3 tablets (450 mg rifampicin and 300 mg isoniazid).
RIFINAH-300: Patients weighing 50 kg or greater: 2 tablets (600 mg rifampicin and 300 mg isoniazid).

All TB medications given 5 times per week

**Duration of treatment at the clinic**

**New case regimen:**
- Months 1-2: H / R / Z / E
- Months 3-6: H/R

**Re-treatment regimen:**
- Months 1-2: H / R / Z / E / S (40 doses of S IM)
- Month 3: H / R / Z / E
- Months 4-8: H / R / E

**Reasons for structure of re-treatment regimen**
- Aim is to achieve relapse-free cure
- Prolonged therapy needed due to presence of dormant / latent organisms (persisters)
- Combination therapy to prevent development of drug resistance
- Single drug resistant mutations may be present at initiation of therapy due to high number of organisms present
- Three bactericidal drugs given in intensive phase will rapidly reduce number of organisms and reduce the risk of resistance developing
- Inclusion of Z allows duration of treatment to be shortened
- E included for duration of treatment to cover for H resistance present

**Common side-effects of TB treatment**

**Severe**
- Jaundice due to drug-induced hepatitis – Z most likely cause – stop all drugs and refer for re-introduction under specialist supervision – E and S not hepatotoxic
- Skin rash – can be caused by all drugs – stop all drugs and refer for re-introduction under specialist supervision
- Hearing loss, vertigo, renal impairment due to S
- Visual loss – due to prolonged use of E – stop E - assessment of colour vision and ophthalmologist review
- Sensory peripheral neuropathy – common – caused by H – can be prevented / treated by pyridoxine – HIV neuropathy identical presentation

**Minor**
- Nausea, vomiting
- Itch
- Athralgia

**Other medications:**
- Pyridoxine 25 – 50 mg daily (to prevent INH neurotoxicity)
- Co-trimoxazole 480 mg 1-2 tabs daily (for PLWH to prevent opportunistic infections, shown to improve survival in RCT)
Operational:
- Notification and registration with TB clinic, cough hygiene
- Directly observed therapy if possible for entire duration of treatment
- Completion of Green Card to record adherence to therapy
- Application for disability grant for duration of therapy (if needed)
- Nutritional assessment

Monitoring

New smear-positive case:
- Repeat sputum smears at the end of month 2 and month 5 - if positive at month 5 register as treatment failure send sputum for culture and DST - review in 6 weeks

Re-treatment smear-positive case:
- Follow-up initial smear and culture status
- Review culture and DST results at 6 weeks – refer if drug resistance present
- Repeat two sputum smears sent at the end of month 3 and month 7
- If smear positive at 3 months - repeat culture
- If smear positive at 7 month register as treatment failure and refer
- Weigh regularly, adjust drug doses

Smear-negative cases:
- Smear-negative PTB and pleural TB: Duration as for smear-positive PTB (new case and retreatment) - clinical reassessment at weeks 2 and 4, with clinical and culture review at week 8. Repeat cultures if necessary. Final clinical review at months 3 and 4. At clinical review assess symptoms and level of functioning.*
- EPTB excluding TBM and TB lymphadenitis: as for smear-positive TB
- TBM and TB lymphadenitis: New case as for smear + PTB, with continuation phase extended by 3 months for total of 9 months Rx (with option of extending to 12 months). Re-treatment case as for smear-negative PTB with continuation phase extended for 4 months to give total of 12 months Rx. Clinical review as for smear negative PTB, with visual acuity checks at months 3, 6, 9, (12 for re-treatments).

*Focal symptoms (including cough), fever, fatigue, weight loss, should have resolved after 8 weeks of treatment. Weight gain implies successful treatment. Level of functioning is determined clinically - successful treatment implies that the patient should be able to return to normal way of life. Untreated HIV infection or post-TB lung disease can make response to treatment more difficult to assess.

HIV-positive patients:
- Repeat CD4 count six monthly after initial count
- Initiate antiretroviral training if CD4 <200 or AIDS-defining diagnosis develops

Follow-up of TB cases at MOPD

The following patients should be seen at MOPD at 4 weeks and 8 weeks if not responding well to treatment.
1. TBM: to review neurological status and assess need for ventriculoperitoneal shunt.
2. Pericardial TB: to assess for features of pericardial tamponade or constriction.
3. Pleural TB: to exclude empyema or malignancy

TB clinic nurses should refer patients in for review if there is failure to thrive after 8 weeks of TB treatment based on:
1. Weight loss
2. Fatigue
3. Persisting focal symptoms (e.g. cough, lymph node enlargement, pleural effusion)

Note: Patients with smear-negative TB should not be referred back to MOPD for chest X-ray at treatment completion UNLESS there are symptoms suggestive of persisting TB (see above).
C. Multidrug Resistant TB (MDRTB)

MDRTB is becoming increasingly common in KwaZulu-Natal. The severity of this problem and its public health implications should not be underestimated.

Definitions of TB drug resistance

**Mono-resistance**: Resistance to one of the first line TB drugs

**Poly-resistance**: Resistance to two or more first line TB drugs

**Multi-drug resistance**: Resistance to isoniazid and rifampicin

**XDRTB**: Resistance to most or all first line and second line TB drugs including isoniazid and rifampicin

**Note**: Patients with mono-resistance or poly-resistance other than multi-drug resistance or XDRTB are frequently cured by standard four-drug therapy. Patients with multi-drug resistance or XDRTB are *never* cured by standard four drug therapy.

Definitions of MDRTB suspect

1. Any patient who is sputum smear positive after 2 months of TB therapy AND culture/sensitivity tests have been sent
2. Any patient who is failing to thrive after 2 months of TB therapy and has signs of a deteriorating focal disease process compatible with tuberculosis AND culture/sensitivity tests have been sent
3. Any TB suspect who has been in contact with a patient known to have MDRTB AND culture/sensitivity tests have been sent

Management of MDRTB suspects:

**Admission:**

MDRTB cases or suspects should preferably be managed at home. **Rationale**: fewer people will come into contact with the patient at home than in a crowded hospital ward.

Please ensure that outpatients have a good sputum specimen sent for culture and DST - label the form very clearly ‘MDRTB suspect’ or ‘MDRTB case’.

MDRTB cases or suspects can **only** be admitted if:

- There is an intercurrent illness (e.g. pneumonia) that needs inpatient treatment

Advanced TB alone is not an indication for admission (infection control risks outweigh benefit to patient).

MDRTB suspects who need admission should be admitted to the isolation cubicle after a Consultant has assessed the case. The Consultant should sign the transfer on the front of the case sheet.

**Note:** It is compulsory that all Healthcare Workers who enter the MDRTB isolation cubicles wear a closely fitted N95 mask.

Only two designated family members can visit the patient in the cubicle wearing compulsory N95 masks (each patient is assigned two N95 masks for visitors)

All suspected MDRTB cases on admission should be taught cough hygiene, taught how to wear a surgical mask and presented to a consultant within 24 hours of admission. If the diagnosis of MRTB suspect is confirmed by the consultant the patient should remain in the isolation ward or cubicle.
Day 1: Enter the patient's name onto the TB suspect register. The patient is started on intravenous coamoxyclav 1.2 g IV 8 hourly with erythromycin 500 mg 6 hourly and TWO sputum specimens are sent for AFB smear. A THIRD specimen is sent for TB culture and DST. All forms must include the patient’s national ID number and contact details.

Day 3: The patient’s case and sputum smear results is reviewed with an infectious diseases consultant.

Day 5 - 7: The patient’s case is reviewed again with in infectious diseases consultant, response to antibiotic therapy is assessed, and a decision whether or not to start empiric MDRTB therapy is made (usually it is NOT started). Safe arrival of the specimen at IALH TB lab must be confirmed by the registrar. ARV therapy is initiated if needed.

Further: If empiric MDRTB therapy is started the patient is kept in the isolation cubicle until the DST becomes available. If empiric MDRTB therapy is not started the patient can be discharged home and asked to return for DST results within 4 to 6 weeks or immediately if deterioration occurs. Family members must receive education and counselling by the TB Coordinator, Infection Control or an appropriately trained person under their supervision:
- Infection risks in the home, details of MDRTB treatment, duration and side-effects
- The patient sleeps alone in room with open window;
- Family members who HIV-infected, diabetic, very young or very old should move out of the house
- The patient follows cough hygiene (coughs into cupped hands that are frequently washed, or a tissue which is thrown away) and wears a surgical mask when in other rooms of the house.

Definition of MDRTB

1. Any patient with a TB culture resistant to both isoniazid and rifampicin

Management of MDRTB

1. All MDRTB suspects should have full traceable (including two active cellphone numbers) contact details in MDRTB suspect register entered by the TB Coordinator (or a designated supervised staff member)
2. All MDRTB suspects or MDRTB cases should be discussed with the doctor on call at King George Hospital, or a medical specialist or infectious diseases specialist.
3. MDRTB suspects or cases should be nursed in the side cubicles of 5B1 and 5F
4. All staff in contact with MDRTB suspects or cases should use fitted N95 masks that can be obtained from the Unit Manager
5. The minimum amount of time an N95 mask can be used for is 7 days of continuous use, the maximum amount of time an N95 mask can be used for is 14 days
6. Less ill patients can be managed as outpatients while waiting for sensitivity results
7. If the decision is made to treat for MDRTB at least three to four effective drugs should be prescribed in consultation with an MDRTB specialist
8. Patients being treated for MDRTB should be transferred to the Doris Goodwin TB Hospital, Richmond Chest or King George V Hospital for ongoing therapy.

Management of poly-resistance other than MDRTB

Treatment of poly-resistance other than MDRTB should be individualized after discussion with a specialist.

Note: A single drug should never be added to a failing regimen