ANTI-TUBERCULOSIS TREATMENT

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OUTLINE

1. Aims of Treatment
2. First-line Anti-tuberculosis Drugs & Drug Dosage
3. PTB in Adults
   - Treatment of new cases
   - Treatment of previously treated cases
4. Fix dose combination (FDC)
5. DOTS
6. Special situation: pregnancy & lactation
AIMS OF TREATMENT OF TUBERCULOSIS

- To cure patient & restore quality of life & productivity
- To prevent death from active TB or its late effects
- To prevent relapse of TB
- To reduce transmission of TB to others
- To prevent the development & transmission of drug resistance TB
How to do it?

- Health education must be given to the patient and family members/carers at the time of starting treatment.

- This should include:-
  - a. nature of the disease
  - b. necessity of strict adherence with the prolonged treatment
  - c. risks of defaulting treatment
  - d. side effects of medication
  - e. risks of transmission and need for respiratory hygiene as well as cough/sneeze etiquette
FIRST-LINE ANTITUBERCULOSIS DRUGS

- Isoniazid (H)
- Rifampicin (R)
- Pyrazinamide (Z)
- Ethambutol (E)
- Streptomycin (S)

Fixed Dose Combination anti-TB drugs (FORECOX-Trac)
- H 75mg + R 150mg + Z 400mg + E 275mg
- Available for Intensive Phase treatment
The three major actions of antituberculosis drugs are:

1) **bactericidal** action, defined as their ability to **kill actively growing bacilli rapidly**, e.g. isoniazid, and to a lesser extent, rifampicin and streptomycin (S);
2) **sterilising** action, defined as their capacity to **kill the semi-dormant organisms**, e.g. rifampicin and pyrazinamide (Z);
3) **prevention of emergence of bacillary resistance** to drugs, e.g. isoniazid and rifampicin; less so for streptomycin, ethambutol (E) and pyrazinamide.
PULMONARY TB (PTB) IN ADULTS

Treatment of new cases

Six-month regimen consisting of two months of daily EHRZ* (2EHRZ) followed by four months of daily HR* (4HR) is recommended.

2EHRZ 4HR
Weight is dynamic
CPG RECOMMENDATION

10 New patients with pulmonary tuberculosis should receive daily 2EHRZ and followed by daily 4HR**. (Grade A)
10 Regimen should contain six months of rifampicin. (Grade A)
10 Rifampicin should be rounded to higher recommended dose if tolerated. (Grade C)
10 If ethambutol is contraindicated, streptomycin can be substituted. (Grade A)
TREATMENT OF PREVIOUSLY TREATED CASES

- (failure, relapse or return after default)

Interruption in the intensive phase:
  - a. If $\geq 14$ days, to restart from the beginning i.e. Day 1
  - b. If $<14$ days, to continue from the last dose

In either (a) or (b), the total number of planned doses for the intensive phase should be given.
TREATMENT OF PREVIOUSLY TREATED CASES, con't

10 Interruption in the maintenance phase:
   10a. If interruption occurs after patient receives 80% of the total planned doses, the treatment may be stopped. If the sputum AFB smear was negative at the initial presentation. If the sputum AFB smear was positive, the treatment should be continued to achieve the total number of planned doses.
   10b. If patient receives <80% of total planned doses and interruption lapse is ≥2 months, restart treatment from the beginning.
   10c. If patient receives <80% of total planned doses and interruption lapse is <2 months, continue treatment from date it stops to complete full course.
Table 3.4  STANDARD REGIMENS FOR PREVIOUSLY TREATED PATIENTS
depending on the availability of routine DST to guide the therapy of
individual retreatment patients

<table>
<thead>
<tr>
<th>DST</th>
<th>Likelihood of MDR (patient registration groupa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routinely available for previously treated patients</td>
<td>High (failureb)</td>
</tr>
<tr>
<td>Rapid molecular-based method</td>
<td>DST results available in 1–2 days confirm or exclude MDR to guide the choice of regimen</td>
</tr>
<tr>
<td>Conventional method</td>
<td>While awaiting DST results:c Empirical MDR regimen</td>
</tr>
<tr>
<td>None (interim)</td>
<td>Empirical MDR regimen</td>
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a The assumption that failure patients have a high likelihood of MDR (and relapse or defaulting patients a medium likelihood) may need to be modified according to the level of MDR in these patient registration groups, as well considerations discussed in section 3.8.

b And other patients in groups with high levels of MDR. One example is patients who develop active TB after known contact with a patient with documented MDR-TB. Patients who are relapsing or returning after defaulting from their second or subsequent course of treatment probably also have a high likelihood of MDR.

c Regimen may be modified once DST results are available (up to 2–3 months after the start of treatment).
Current evidence suggests that the optimal duration of treatment for sputum positive PTB is at least six months.

- EPTB: meningeal: one year
- Joint & spine: 6-9 months
- LN: 6 months (Nice guideline)
REGIMEN DURING THE MAINTENANCE PHASE OF TREATMENT….

- In new patients with PTB, WHO recommends **daily** dosing throughout the course of antiTB treatment.

- **Thrice weekly** maintenance phase is an option provided that each dose is directly observed and patient has improved clinically.

- A maintenance phase with **twice weekly** dosing **is not recommended** since missing one dose means the patient receives only half the total dose for that week.
FIXED-DOSE COMBINATIONS (FDCS)

FDC drugs incorporate two or more drugs in single tablet and offer reduction in number of pills that need to be consumed.

The following FDC preparations are registered in Malaysia:-

- Forecox-Trac Film Coated Tab: Isoniazid, Rifampicin, Ethambutol and Pyrazinamide
- Rimactazid 300 Sugar Coated Tab: Isoniazid and Rifampicin
- Rmcure 3-FDC Film Coated Tab: Isoniazid, Rifampicin and Pyrazinamide
- Akurit-Z Tab: Isoniazid, Rifampin (Rifampicin) and Pyrazinamide
- Akurit Tab: Isoniazid and Rifampin (Rifampicin)
- Akurit-Z Kid Dispersible Tab: Isoniazid, Rifampin (Rifampicin) and Pyrazinamide
- Akurit-4: Ethambutol, Isoniazid, Rifampin (Rifampicin) and Pyrazinamide
FDC…

The recommended dosages for the two FDCs are:-

1. 30 - 37 kg body weight: 2 tablets daily
2. 38 - 54 kg body weight: 3 tablets daily
3. 55 - 70 kg body weight: 4 tablets daily
4. More than 70 kg body weight: 5 tablets daily
ADVANTAGE OF FDC

1. Reduce the risk of non-compliance by 17% and consequently improve effectiveness of therapy.
2. Smaller number of tablets to be ingested may also encourage patient adherence.
3. RCTs showed that FDCs are as effective as separate-drug regimens for the treatment of tuberculosis.
4. Prescription errors are likely to be less frequent for FDCs due to easy adjustment of dosage according to patient weight.
5. In terms of bioavailability, FDCs are proven to be bioequivalent to separate-drugs formulations at the same dose levels.
Corticosteroid in TB

- Proven benefit in Tb meningitis and pericarditis
- No one fix recommendation dose, dexamethasone vs steroid, high dose tapering off over 6-12 weeks.
- Also useful in uveitis and urinary TB
- (Dose may be 20 mg tds-qid 4-6 weeks)
- Caution: immunosuppression, sugar control, bioavailability of rifampicin may be reduced.
DIRECTLY OBSERVED TREATMENT (DOT)

“… an observer* watches the patient swallowing their tablets, …

… patient take the **right** antituberculosis **drug**, in the **right doses**, at the **right interval**.”

The observer may be a health care worker or a trained and supervised community member
WHO launched Direct Observed Therapy, Short Course (DOTS) in 1995. This strategy combines drug treatment with political commitment, sputum smear microscopy for diagnosis and directly observed therapy (DOT) to ensure adherence and good management practice.

DOT increased the completion rate compared to those on SAT.

The practice of DOT in Malaysia was reported to be 97% (ranging from 93% to 100%).

A study in Thailand in 2002, only 65% to 89% of those assigned actually watched the patients taking the drugs.

Involve process of negotiation and support, incorporating patients’ characteristics and choices.

A controlled trial in Tanzania comparing patient-centred approach where patient was given the choice to receive treatment at home observed by a supporter of their own choice vs daily treatment at health facilities observed by healthcare worker showed a better treatment success rate in the patient-centred approach.
What to consider when starting anti-tb treatment

- **Weight**
  - must calculate anti-TB dose based on patients weight
- **Creat level**
  - especially patient with low weight, with normal value Sr creat (may need to calculate eGFR)
  - if renal impairment may need to give renal dose anti-TB
- **Patient general well being / social support**
- **Other co-morbidities**
- **Drug Interactions**
  - ask about drug history
- **Ensure DOTS**
RIFAMPICIN AND ORAL CONTRACEPTIVE PILLS

Women using oral contraceptives, should either use an oral contraceptive pill containing a higher dose of estrogen (50 μg) or use a nonhormonal method of contraception may be used throughout rifampicin treatment and for at least one month subsequently.
Breast feeding and pregnancy

• Untreated tuberculosis >>> greater hazard to a pregnant woman and her fetus than does treatment of her disease.
• BF is allowed, as far as mother is not infective and treated.
• Potential toxic effects of drugs delivered in breast milk have not been reported.
• Pyridoxine supplement in pregnancy should be at a dose of 50 mg/day (instead of 25 mg/day).
Should I extend the intensive phase?

- Get the C&S result back!
- Repeat the C&S!

- In patients (newly diagnosed) treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is **not recommended** *(WHO TB guideline 2009)*
"Totally Drug-Resistant" tuberculosis: a WHO consultation on the diagnostic definition and treatment options

21-22 March 2012

Background

Within a year of the first reports of extensively resistant TB (XDR-TB) in 2006, isolated cases were reported in Italy that had resistance to all first-line anti-TB drugs (FLD) and second-line anti-TB drugs (SLD) that were tested. In 2009, a cohort of 15 patients in Iran was reported which were resistant to all anti-TB drugs tested. The terms ‘extremely drug resistant’ (‘XXDR-TB’) and ‘totally drug-resistant TB’ (‘TDR-TB’) were given by the respective authors reporting this group of patients. Recently, a further 4 patients from India with ‘totally drug resistant tuberculosis’ (TDR-TB) were described, with subsequent media reports of a further 8 cases.

The term ‘totally drug resistant’ has not been clearly defined for tuberculosis. While the concept of ‘total drug resistance’ is easily understood in general terms, in practice, in vitro drug susceptibility testing (DST) is technically challenging. XDR-TB is much more common than TDR-TB, which is rare.
What do you *EXPECT* in your lifetime?

What will you *DO*?

**WORLD TB DAY** 24 MARCH 2013

Patient empowerment  
Adherence  
Education
Thank you