GUIDELINE FOR SECOND LINE ANTI-TUBERCULOUS TREATMENT IN PAKISTAN

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The emergence of resistant strains of Mycobacterium Tuberculosis is becoming a continual challenge for Physicians and has made it necessary to be more vigilant and concerned about second line anti tuberculous drugs. Patients retreated with 5 drugs regimen in the initial phase for 3 months and then 2 months as a continuation phase with the first line anti Tuberculous drugs, still remaining AFB smear positive, can be labelled as resistant tuberculosis. The overall incidence of resistant tuberculosis is increasing by variable numbers in different countries.

In Pakistan the reasons for multi drug resistant strains are mainly poverty malnutrition, inappropriate combination and dosage of anti tuberculous drugs lack of patients compliance and infection with initial drug resistant myco bacteria. Drugs used as second line treatment, are Kanamycin, Ethionamide, Prothionamide Cycloserine and Capreomycin. Drugs like ciprofloxacin, ofloxacin, clofamazin and clarithromycin are under trial and still needs justification for their regular use.

While recommending second live treatment always 3-4 new effective drugs should be added, to prevent resistance, starting with 3-4 months of intensive phase and then a continuation phase, to complete 24 months. Cost of the second time treatment makes a lot of difference to poor patients as it is quite costlier than the first line drugs. Proper follow up of patients on second line drugs, and hospitalization for the whole intensive phase to ensure a fully supervised treatment is necessary. Switching over to continuation phase depends on conversion of the sputum smear to negative at least by the end of 6 months of intensive phase treatment. It will be of no use to continue ATT if the sputum smears are positive for AFB by the end of 6 months intensive phase therapy, all that is needed for such patients will be a Psychiatric help and awareness of the family.

Key words: Resistant Pulmonary Tuberculosis
Second line treatment

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DEFINITION OF RESISTANT PULMONARY TUBERCULOSIS:

In our setting it is difficult to define resistant tuberculosis, the reason being non-availability of reliable laboratories. So the definition should be based on clinical grounds i.e. Patients who after five months of retreatment regimen, (1) i.e

2 months intensive phase with 5 drugs i.e Streptomycin, I.N.H. Rifampicin, Pyrazinamide and Ethambutol SHRZE and 2 more months of intensive phase with 4 drugs i.e RHEZ, and one month of continuation phase with RHE who are

SHRZE = Streptomycin INH
Rifampicin, Pyrazinamide, Ethambutol
K = Kanamycin H = Isoniazid (INH)
Eth = Ethionamide Th = Thiacetazone
Cs = Cycloserine Of = Ofloxacin

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still AFB smear +ve can be labelled as resistant tuberculosis.

INCIDENCE OF RESISTANT TUBERCULOSIS

In Hong Kong the incidence of resistant tuberculosis is 20%, while in the U.S.A, it used to be 4% 15 years ago, but now it is rising. Kathleen & colleagues found an overall resistance rate of 33% with resistance of INH 25%, Rifampicin 20% and combined INH-Rifampicin resistance 16%. Chawla & colleagues found an overall resistance rate of 30.9% to one or more drug with combined resistance to INH-Rifampicin 30.2%, in a study conducted at King County Hospital in Brooklyn.

In Pakistan, multidrug-resistant tuberculosis appear to be on the rise although at present we do not have concrete data regarding resistant tuberculosis. The causes of this rise are:

1) Over the counter sale of Anti-tuberculous drugs.
2) Poverty, malnutrition, overcrowding.
3) Inappropriate combination and dosage of Anti-tuberculous drugs.
4) Inadequate period of treatment.
5) Treatment abandoned because of side effects of drugs.
6) Nonavailability of drugs due to financial constraints.
7) Infection with initial drug resistant Mycobacteria.
8) H.I.V epidemics
9) Drug abusers.

T.B is purely emperical. It is suggested that proper screening should be conducted to assess the situation.

MANAGEMENT

Management of tuberculosis is not an easy task, because nowadays patients come to the Chest specialist after shopping from multiple physicians and history of irregular intake of anti tuberculous drugs. In these cases, there is still a chance of complete cure if they take their prescribed drugs with religious fervour. Even then there is a group of patients who because of their irregular intake or initial resistance cannot be cured with the first line drugs. They need second line drugs as the last resorts.

SELECTION OF PATIENT : (HOW TO ESTABLISH TREATMENT FAILURE ON FIRST LINE DRUGS)

Patients who after five months of retreatment regimen (CAT. II) do not convert should be considered for second line treatment.

PRIORITIES IN SELECTION OF PATIENT

i) Young patients.
ii) Earning member of the family.
iii) Key member of the family.
iv) Patients who can personally afford the cost of full course i-e two years of second line treatment and agrees to continue treatment for the full two years.

SECOND LINE DRUGS

i) Inj. Kanamycin.
ii) Ethionamide tab.
iii) Prothionamide.
iv) Cycloserine cap.
v) Inj. Capreomycin
vi) Viomycin.
vii) P.A.S tab.
viii) Thiacetazine.tab.

The last two drugs i-e Thiacetazine and P.A.S are actually first line drugs but because of their nonavailability are not frequently used in Pakistan as first line drugs.

**TERTIARY / RESERACH DRUGS**

i) Inj. Amikacin.

ii) Quinolones e.g Ciprofloxacin, ofloxacin

iii) Clofazimine

iv) Klaricid.

v) Rifamycin.

vi) Penems.

<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>PRICE/UNIT</strong></th>
<th><strong>DAYS</strong></th>
<th><strong>TOTAL AMOUNT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inj. Kanamycin IG/day</td>
<td>Rs. 8/-</td>
<td>90</td>
<td>720/-</td>
</tr>
<tr>
<td>Tab. Ethionamide 3/day</td>
<td>Rs. 13/-</td>
<td>720</td>
<td>28080/-</td>
</tr>
<tr>
<td>Cap. Cycloserine 3/day</td>
<td>Rs. 32/-</td>
<td>720</td>
<td>69120/-</td>
</tr>
<tr>
<td>Tab. Ofloxacin 4/day</td>
<td>Rs. 28/-</td>
<td>720</td>
<td>80640/-</td>
</tr>
<tr>
<td>Inj. Amikacine IG/day</td>
<td>Rs. 708/-</td>
<td>90</td>
<td>63720/-</td>
</tr>
</tbody>
</table>

The total cost of treatment varies greatly depending on the regimen used for the particular patient.

**RECOMMENDED REGIMEN**

To prescribe any regimen certain rules should be followed:

i) Proper treatment history is vital for the selection of proper regimen.

ii) Never add single new drug because this will lead to resistance to the newly added drug.

**AVAILABILITY AND COST**

Most of the second line drugs are not available freely in the market. The few which are available are smuggled from neighbouring countries and are very expensive, their regular supply cannot be ensured. Beside their price fluctuates markedly depending on the availability in the market. The cost of some of the drugs which are available in Pakistan are:

iii) Always add 3-4 new effective drugs to prevent resistance.

iv) Consideration should be given to the cross-resistance between drugs, eg Thiacetzone and Ethionamide, viomycin and vapiromycin.

v) Select that regimen which patient can afford, and which is effective.

The following regimens are recommended:
REGIMEN | INT. PHASE | CONT. PHASE
---|---|---
I | 3-4 K+Eth. + H + Th (daily) | Eth. + H + Th. (daily) to complete 24 months
II | 3-4 K+Eth. + H + Th. + Cs (daily) | Eth. + Th. + H + Cs (daily) to complete 24 months.

COST OF THESE REGIMENS:

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DRUGS</th>
<th>DAYS</th>
<th>COST</th>
<th>TOTAL COST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kanamycin Inj</td>
<td>90</td>
<td>Rs. 720/-</td>
<td>Rs. 28800/-</td>
</tr>
<tr>
<td></td>
<td>Ethionamide tab.</td>
<td>720</td>
<td>Rs. 28080/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Th. H tab.</td>
<td>720</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-</td>
<td>Kanamycin Inj</td>
<td>90</td>
<td>Rs. 720/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethionamide tab.</td>
<td>720</td>
<td>Rs. 28080/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycloserine cap.</td>
<td>720</td>
<td>Rs. 69120/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Th. H tab.</td>
<td>720</td>
<td>----</td>
<td>Rs. 97920/-</td>
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<tr>
<td>III-</td>
<td>Kanamycin Inj.</td>
<td>90</td>
<td>Rs. 720/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>720</td>
<td>Rs. 28080/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycloserine cap.</td>
<td>720</td>
<td>Rs. 69120/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I.N.H. tab.</td>
<td>720</td>
<td>Rs. 540/-</td>
<td>Rs. 179100/-</td>
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<tr>
<td></td>
<td>Ofloxacin</td>
<td>720</td>
<td>Rs. 80640/-</td>
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The cost of Thiacetazole-INH combined tablets has not been included because of nonavailability in open market. These are supplied by world health organization free of cost, that is why their cost is not included.

TOTAL COST OF FIRST LINE ANTITUBERCULAR DRUGS (5 DRUGS):

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PRICE PER UNIT</th>
<th>DAYS</th>
<th>TOTAL COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin 450</td>
<td>Rs. 5/-</td>
<td>240</td>
<td>Rs. 1200/-</td>
</tr>
<tr>
<td>I.N.H. 100</td>
<td>Rs. 0.25</td>
<td>240</td>
<td>Rs. 180/-</td>
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<tr>
<td>Myambutol 400</td>
<td>Rs. 1.20</td>
<td>240</td>
<td>Rs. 576/-</td>
</tr>
<tr>
<td>Streptomycin IG</td>
<td>Rs. 5.50</td>
<td>90</td>
<td>Rs. 495/-</td>
</tr>
<tr>
<td>Pyrazinamide 500</td>
<td>Rs. 1.35</td>
<td>90</td>
<td>Rs. 365/-</td>
</tr>
</tbody>
</table>
The total cost of very effective first line drugs for 8 months is 2816/- rupees (CAT. II patients). This cost further decreases to 1953 rupees (2SRHZ 6RH) and Rs. 1767/- (2REHZ 6RH) for Cat I patients. These figures indicate how cost effective is to treat T.B patients in their early stage.

ROLE OF SPUTUM SENSITIVITY

At present there is no laboratory in the city on which we can rely because reference laboratory facilities do not exist in Pakistan. Therefore the Physician has to rely mainly on clinical acumen and experience.

DURATION OF SECOND LINE A.T.T

It varies from 18-24 months.

FOLLOW-UP OF PATIENT

All patients on second line must be hospitalised during the whole period of intensive phase to ensure fully supervised treatment and ease in managing any complication if they arise. Regular drug intake under supervision (DOT) will ensure best possible effect of the drugs.

Sputum direct smear examination every month is recommended throughout treatment.

Chest X-ray every three month is recommended

During continuation phase, the patient should be followed every month by the same Doctor who treated him/her during intensive phase.

If the sputum is negative at the end of intensive phase, switch over to continuation phase, which include at least 3 drugs. If the sputum is positive at the end of intensive phase extend the intensive phase for one more month. At the end of 4 months, if sputum is negative, switch over to continuation phase. If sputum is positive at the end of 4 months, continue intensive phase. It is of no use to continue A.T.T. if sputum is still positive at the end of 6 month.

POST-TREATMENT FOLLOW-UP

Every 3 months upto two years.

HEALTH EDUCATION

Before starting second line drug treatment, the patient and his family members should be properly briefed. They should be informed that this is probably the LAST CHANCE OF CURE and the patient and family members should ensure that the medicines are taken regularly as prescribed and clinical test and examination are carried out as frequently as the Physician suggests, otherwise the effectiveness of second line drugs would also be compromised and not only the patients chances of survival will be diminished but his/her family members and other people who may have been infected by him or her, are also likely to develop the same resistant type of tuberculosis from the very first day and they will loose their chance of cure and they will spread the resistant type of tuberculosis in the community thus continuing the vicious circle at a greater speed.

The patient’s family should also be told about the high cost of drugs and the fact that if the patient discontinues treatment after sometime, the total effectiveness of the drugs decreases and the money spent on the patient goes down the drain.
WHAT TO DO WITH PATIENTS WHO FAIL ON THIS SECOND LINE REGIMEN OR WHO REFUSE TREATMENT OR SIMPLY CANNOT AFFORD TREATMENT

Patients who after 6 months of regular intake of second line drugs donot respond, should be seen by a Psychiatrist to help ease the trauma of suffering from incurable ailment. They and their family members should be taught proper precautions, sanitary measures to prevent the further spread of disease into the community. The patients who refuse treatment or simply cannot afford the treatment or those who take the drugs for few days but loose heart due to the side effects, should be advised of the consequences of their action. They or their family members should be convinced of the need for treatment and that this is probably their last chance of cure and should contact some social or charitable NGO’s for assistance and all attempt should be made to save their lives. All patients and their family members should be taught proper precautions and sanitary measures to prevent the further spread of disease in the community.

REFERENCES:


