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## *Selected Summaries*

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### **Chemotherapy for Tuberculosis**

*[Official Statement of American Thoracic Society, endorsed by the American Academy of Pediatrics, April 1993. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Resp Crit Care Med 1994,149:1359-1374.]*

1. A 6 month regimen consisting of Isoniazid, Rifampin and Pyrazinamide given for 2 mo followed by INH and Rifampin for 4 months is the preferred treatment for patients with fully susceptible organisms who adhere to the treatment. Ethambutol (or Streptomycin) should be included in the initial regimen until the drug susceptibility is known or if there is >4% initial resistance to INH in the community. This 4 drug, 6 months regimen is effective even when the infecting organism is resistant to INH. This recommendation applies to both HIV infected and uninfected persons. However, in the presence of HIV infection it is critically important to assess the clinical and bacteriological response. If there is any evidence of a slow or suboptimal response, therapy should be prolonged as judged on a case by case basis.

2. Alternatively, a 9 month regimen of INH and Rifampin is acceptable for persons who cannot and should not take Pyrazinamide. Ethambutol (or Streptomycin) should also be included if INH resistance is expected till susceptibility studies are available. If INH resistance is

confirmed, Rifampin and Ethambutol should be continued for at least 12 months.

3. Consideration should be given to treating all patients with directly observed therapy.

4. Multiple drug resistant tuberculosis (*i.e.*, resistant to at least rifampin and INH) presents difficult treatment problems. Treatment must be individualized and based on susceptibility studies. In such cases, consultation with an expert in tuberculosis is recommended.

5. Children should be managed in essentially the same ways as adults using appropriately adjusted doses of drugs. The document addresses specific important differences between management of adults and children.

6. Tuberculosis in infants and children younger than 4 years of age is much more likely to disseminate; therefore, prompt and vigorous treatment should be started when the diagnosis is suspected.

7. Primary intrathoracic tuberculosis (parenchymal infiltration, hilar lymphadenopathy or both in a child with significant PPD reaction) should be treated in the same manner as pulmonary tuberculosis. However, when drug resistance is unlikely, treatment with 2RHZ/4RH is sufficient.

8. Extra pulmonary tuberculosis should be managed according to the principles and With the drugs outlined for the pulmonary tuberculosis, except for children who have miliary disseminated disease, bone or joint involvement

or tuberculous meningitis who should receive a minimum of 12 month of therapy.

9. The major determinant of the outcome of treatment is patient adherence to treatment.

10. Preventive therapy with INH given for 6 to 12 months is effective in decreasing the risk of future tuberculosis in adults and children with tuberculosis infection demonstrated by a positive skin reaction.

11. Twelve months of preventive therapy is recommended for adults and children with HIV infection and other conditions associated with immunosuppression. The American Academy of Pediatrics recommends that the children without any immunosuppression should get 9 months of preventive therapy.

12. In persons suspected to be infected with Isoniazid resistant organisms (*e.g.*, close contacts of a confirmed INH resistant case) should be treated with Rifampin (with or without ethambutol) rather than with INH, given for a period of 9 months. In persons likely to be infected with bacilli resistant to both INH and Rifampin, observation without preventive therapy has usually been recommended (except in cases at high risk of developing the disease) because no other drugs have been evaluated for preventive therapy.

### Comments

The recommendations given above are exhaustive and based on the present scientific research and data. The present strategy of tuberculosis management in our country is replete with multiple drug regimens and durations. The initial

INH resistance in the country is estimated to be around 10-12% (WHO unpublished data). It may, therefore, be desirable to adopt an initial 4 drug regimen for our pediatric patients. There is an urgent need to rationalize and to provide guidelines to this effect for the Indian population. This assumes further importance due to the renewed National Tuberculosis Program being launched in the country. Under the revised strategy of the Government, in which the cost of therapy is obviously an important consideration, 12 months INH and Thiacetazone therapy or 2RHZ/2RH has been recommended for pediatric sputum negative patients. The Indian Academy of Pediatrics should take a lead and provide uniform guidelines based on a rational balance of the "optimal" and the "feasible".

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*[Weis SE, Slocum PC, Blais FX, King B, Nunn M, Natney B, Gomez E, Foresman BH. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med 1994, 28:1179-1184.]*

This study investigated the hypothesis that a major reason for the development of resistant infections and relapse in tuberculosis is poor compliance with medical regimens. Information was collected on all patients with positive cultures for *Mycobacterium tuberculosis*.

*cobacterium tuberculosis* from January 1, 1980, through December 31, 1992. Through October 1986, patients received a traditional, unsupervised drug regimen. Beginning in November 1986, nearly all patients received therapy under direct observation by health personnel.

A total of 407 episodes in which patients received traditional treatment for tuberculosis (January 1980 through October 1986) were compared with 581 episodes in which therapy was directly observed (November 1986 through December 1992). Despite higher rates of intravenous drug use and homelessness and an increasing rate of tuberculosis during this 13 year period, the frequency of primary drug resistance decreased from 13% to 6.7% ( $p < 0.001$ ) after the institution of direct observation of therapy, and the frequency of acquired resistance declined from 14% to 2.1% ( $p < 0.001$ ). The relapse rate decreased from 20.9% to 5.5% ( $p < 0.001$ ) and the number of relapses with multidrug-resistant organisms decreased from 25 to 5 ( $p < 0.001$ ). It was concluded that the administration of therapy for *M. tuberculosis* infection under direct observation leads to signifi-

cant reductions in the frequency of primary drug resistance, acquired drug resistance, and relapse.

### Comments

This report has confirmed the vital role of drug regimen compliance in ensuring successful chemotherapy for tuberculosis. Even in a developed country setting, poor drug compliance is an important problem and is responsible for a significant proportion of primary drug resistance, acquired drug resistance, and relapse in tuberculosis. The magnitude of the problem is likely to be higher in our setting where the cost of therapy and illiteracy aggravate this situation. Obviously, directly observed therapy in our set up is not feasible and at best, we can only patiently explain and stress the importance of strict adherence to the drug regimen to the parents. Further, poor compliance must be carefully excluded before putting a label of resistant tuberculosis or relapse.

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