

Factors Associated with Treatment Failure in Childhood Tuberculosis

SINDHU SIVANANDAN, MANDEEP WALIA, RAKESH LODHA AND S K KABRA

From the Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India.

Correspondence to: Dr S K Kabra, Department of Pediatrics, AIIMS, New Delhi 110 02, India.

E-mail: skkabra@hotmail.com

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ABSTRACT

We retrospectively reviewed records of 541 children (315 boys) suffering from tuberculosis, median age 95 (range 2-180) months, to determine factors associated with treatment failure. 256 (47.3%) children had pulmonary tuberculosis (PTB) while 285 (52.7%) had extrapulmonary tuberculosis (EPTB). 459 (84.8%) children were cured and 82 (15.5%) had treatment failure. On bivariate analysis, AFB positivity [OR= 2.13 (95% CI 1.18- 3.85)], non-receipt of BCG vaccination during infancy [OR=1.73 (1.02- 2.91)] and EPTB [1.9 (1.16- 3.11)] were associated with treatment failure. On multivariate analysis, only extrapulmonary tuberculosis was significantly associated with treatment failure.

Key words: *BCG, Children, Extrapulmonary tuberculosis, Short course chemotherapy, Tuberculosis.*

INTRODUCTION

Childhood tuberculosis represents a sentinel event in the community suggesting recent transmission from an infectious adult with tuberculosis(1). The main tuberculosis control strategy aims at diagnosis and short course chemotherapy of smear-positive tuberculosis patients(2). Short course chemotherapy is also the standard of care for children with tuberculosis. However, the factors influencing outcome of children with tuberculosis have not been studied well in the developing countries. In this report, we present our analysis of factors affecting the outcome in children with tuberculosis treated with short-course chemotherapy.

METHODS

A chart review of all the children diagnosed as having tuberculosis and treated at our institution between January 2000 and June 2005 was conducted. The demographic details, clinical features, laboratory investigations and outcome were recorded. Weight for age 'z' scores and weight for

height 'z' scores were calculated as per CDC 2000 standards(3). The details of diagnostic criteria, categorization and type of tuberculosis, treatment and follow-up were as described in our earlier report(4). Cure was defined at the end of treatment course as the absence of clinical symptoms and regression of >2/3 of radiological lesion. Failure was defined as either extension of regimen or a change of regimen, based on clinical and radiological response to therapy.

Bivariate analysis followed by multivariate analysis was performed using STATA 7.0 (Stata Corp, College Station, TX) software with the dependent variable being outcome (*i.e.* cured or failure).

RESULTS

A total of 541 children (315 boys, 58%) with tuberculosis were included in the analysis. The median age was 95 (range 2-180) months; 391 (76%) had received BCG vaccination and 225 (42%) had history of contact with TB patient in the family. 256

(47%) children had pulmonary tuberculosis while 285 (53%) had extrapulmonary tuberculosis (**Table I**). Tuberculin test was positive in 300 out of 455 (66%) patients and AFB was identified in 71 (15%) patients.

Out of 541 children, 459 (84.8%) were cured with primary regimen assigned to them. Treatment failure was recorded in 82 (15.2%) children, of these; the regimen was extended in 69 and changed in 13. Overall cure rate for pulmonary and extrapulmonary tuberculosis was 89% (228/256) and 81% (231/285), respectively.

The patients in cure group and failure group did not differ in demographic and laboratory parameters (data not shown). On bivariate analysis, AFB positivity [OR = 2.13 (95% CI 1.18-3.85)], non-receipt of BCG vaccination during infancy [OR=1.73 (1.02-2.91)] and extra pulmonary tuberculosis [OR=1.9 (1.16-3.11)] were associated with treatment failure. On multivariate analysis, only extrapulmonary tuberculosis [OR=1.72 (1.01-2.92)] was significantly associated with failure. Non receipt of BCG [OR 1.58(0.92-2.70)] showed a trend but did not reach statistical significance.

DISCUSSION

Factors associated with failure of therapy in children

with tuberculosis included AFB positivity at diagnosis, non-receipt of BCG vaccination and extrapulmonary tuberculosis; with extrapulmonary tuberculosis being the only major contributor.

AFB positivity at time of diagnosis as one of the determinant of outcome suggests either the disease was extensive or drug resistant. Another possibility may be that there was false diagnosis of tuberculosis in children who were negative for AFB. The fact that AFB positivity was more commonly seen in lymph node tuberculosis and only a small proportion required change of regimen, rules out possibility of extensive and drug resistant disease. Although it cannot be ruled out, the chances of a false diagnosis of tuberculosis are very minimal as we follow a strict protocol in our clinic for diagnosis and treatment of tuberculosis. It is evident from the fact that out of 964 children referred during study period, 134 patients were excluded from analysis as they were assessed not to have tuberculosis.

BCG has not been studied in relation to outcome of tuberculosis in children. Colditz, *et al.*(5), in a meta-analysis, found overall protective effect of BCG as 50% against TB infections. A study from adult patients from Gambia reported that none of the patients with BCG scar died in contrast to 17.5% of those who did not have the scar(6). One possible

TABLE I CLINICAL PROFILE AND OUTCOME OF TREATMENT OF CHILDHOOD TUBERCULOSIS

Diagnosis	Total	Cured	Treatment extension	Change of regimen
Primary pulmonary complex	98	88	9	1
Progressive primary disease	155	138	15	2
Cavitatory tuberculosis	3	2	1	0
Miliary tuberculosis	11	9	2	0
Pleural effusion	30	26	4	0
Tubercular lymphadenitis	153	124	22	7
Abdominal tuberculoasis	19	17	2	0
Osteoarticular tuberculosis	22	18	3	1
Tuberculoma brain	10	8	0	2
Tubercular meningitis	4	4	0	0
Disseminated tuberculosis	30	20	10	0
Pericardial tuberculosis	3	3	0	0
Genitourinary tuberculosis	3	2	1	0
Total	541	459	69	13

WHAT THIS STUDY ADDS?

- Extrapulmonary tuberculosis, nonreceipt of BCG during infancy and AFB positivity at the time of diagnosis may be associated with increased failure rates in treatment of childhood tuberculosis.

explanation offered by the authors was that BCG might have limited the hematogenous spread, thus facilitating cure. Studies in mice indicate that prior immunization enhances macrophage phagocytosis and CD4 T-helper cell activity to contain mycobacterial dissemination(7).

One of the reasons for higher chance of failure in extrapulmonary tuberculosis may be false perception of non-response/failure as in lymph node tuberculosis. Affected lymph nodes may enlarge while patients are receiving appropriate therapy or after the end of treatment, without any evidence of bacteriological relapse(8-10). In the present study we tried to minimize false perception of treatment failure. Children with non resolution of lymphnode or reappearance of new nodes on treatment were labeled as failure only if they had systemic manifestations (weight loss, fever) along with evidence of tuberculosis (granuloma/ AFB) on FNAC.

The major limitation of the study is its retrospective nature. The decision to label a cure or failure was based on clinical and imaging findings alone in many cases. In the absence of demonstration of AFB among those who required either a change or extension of regime, we do not know the exact contribution of primary drug resistance. Adherence to treatment was not documented actively as the patients received domiciliary treatment. The measures to ensure adherence were providing medicines for a period of one month on each visit and asking the parents/caregiver about the medications.

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REFERENCES

1. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. *Lancet Infect Dis* 2003; 3: 624-632.
2. World Health Organization. Monitoring progress in TB control. http://www.who.int/tb/publications/global_report/2006/results/en/index.html. Accessed on February 10, 2008.
3. Centers for Disease Control and Prevention. Epi Info(TM)- Database and statistics software for public health professionals. 2004.
4. Kabra SK, Lodha R, Seth V. Category based treatment of tuberculosis in children. *Indian Pediatr* 2004; 41: 927-937.
5. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, *et al.* Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA* 1994; 271: 698-702.
6. Corrah T, Byass P, Jaffar S, Thomas V, Bouchier V, Stanford JL, *et al.* Prior BCG vaccination improves survival of Gambian patients treated for pulmonary tuberculosis. *Trop Med Int Health* 2000; 5: 413-417.
7. Ordway D, Harton M, Henao-Tamayo M, Montoya R, Orme IM, Gonzalez-Juarrero M. Enhanced macrophage activity in granulomatous lesions of immune mice challenged with *Mycobacterium tuberculosis*. *J Immunol* 2006; 176: 4931-4939.
8. British Thoracic Society Research Committee. Six-months versus nine-months chemotherapy for tuberculosis of lymph nodes. *Respir Med* 1992; 86: 15-19.
9. Campbell IA, Dyson AJ. Lymph node tuberculosis: a comparison of various methods of treatment. *Tubercle* 1977; 58: 171-179.
10. Campbell IA, Ormerod LP, Friend JA, Jenkins PA, Prescott RJ. Six months versus nine months chemotherapy for tuberculosis of lymph nodes: final results. *Respir Med* 1993; 87: 621-623.