Supplement-Indian J Pediatr 2000; 67: S34-S40

Management of Non-Pulmonary Forms of Tuberculosis : Review of TRC Studies over Two Decades

Rani Balasubramanian and Rajeswari Ramachandran

Tuberculosis Research Centre, Indian Council of *Medical Research, Chetput, Chennai*

Abstract. Tuberculosis Research Centre, Chennai has been conducting randomized controlled clinical trials in both adults and children (n = 1015) in various non-pulmonary forms of tuberculosis, for the last two decades. This communication discusses the salient findings of these studies. The important finding is that short course chemotherapeutic regimens have been proven to be highly effective in tuberculosis of spine, superficial tuberculous lymphadenitis, abdominal tuberculosis, brain tuberculoma and Potts paraplegia. However, in tuberculous meningitis, the outcome appears to be directly related to the stage of the disease on admission. The intermittent regimens have been found to be as effective as daily regimens. The other important aspects highlighted are the need to obtain bacteriological/histo-pathological confirmation by resorting to relevant diagnostic procedures, value of Mantoux as a diagnostic tool and role of surgery.

Key words *: Extra-pulmonary TB ; Short-course chemotherapy, TB lymphadenitis.*

The clinical manifestations of tuberculosis (TB) are of two types: pulmonary and non-pulmonary forms of TB (NPFTB), pulmonary being the commonest. In NPFTB highly vascular areas like lymph nodes, meninges, kidney, spine and growing ends of the bones are usually affected. The other sites are the pleura, pericardium, peritoneum, liver, gastro-intestinal tract, genito-urinary tract and skin. The precise diagnosis of NPFTB is a challenge to physicians and delay in diagnosis can be fatal or lead to life threatening sequelae in severe forms like meningeal TB.

Recently the diagnosis and treatment of non-pulmonary forms of TB are gaining importance in developed and developing countries. In HIV infected individuals, meningeal, gastro-intestinal tract and lymphnodal TB are more often reported (up to 70%)[1]. The increase in prevalence of NPFTB in the USA and the UK is largely attributed to immigration and HIV infection[2]. In India the prevalence of NPFTB in the HIV infected individuals is not known. The surveys in the UK have demonstrated ethnic differences in the involvement of different organs with tuberculosis[3].

There is ambiguity regarding the most appropriate combination of drugs, duration of chemotherapy and the role of surgery in the treatment of NPFTB[4,5]. The difficulty in evolving a clear cut 'end point' in assessing the efficacy of treatment of NPFTB has led to varying durations of treatment (6 to 24 months) and there have been relatively few controlled clinical trials in NPFTB[6]. The principles involved in diagnosis and management are evolved mainly from the experience gained from randomised controlled clinical trials (RCTs) on pulmonary TB.

Tuberculosis Research Centre undertook several studies on NPFTB such as spinal TB, Pott's paraplegia, tuberculous meningitis, brain tuberculoma, tuberculous lymphadenitis and abdominal TB[7-13]. The common objective was to assess the efficacy of short course chemotherapy (SCC) in NPFTB. The results at the end of the treatment and relapses over a varying period of 3 to 10 years were assessed systematically. In some of the studies like TB spine and abdominal TB the role of surgery was also addressed. The individual reports of these trials discuss the diagnostic criteria used, treatment regimens tried and the outcome in detail. This paper discusses the diagnostic and management challenges faced while treating NPFTB based on the observations of these trials.

MATERIALS & METHODS

The collaborating institutions were from the Government teaching hospitals of Chennai. Patients diagnosed on clinical grounds were referred to TB Research Centre for investigations. All the studies had protocols defining admission criteria, exclusion criteria, treatment policies, period of follow-up, list of investigations, (pre-treatment and the follow-up), periodic assessments (clinical and radiological), and criteria for favourable response at the end of treatment, relapse and failures. Wherever indicated, smear, culture and sensitivity tests were undertaken for sputum, pus, urine and specimens removed during surgery.

After investigations, eligible patients with definitive criteria were admitted to respective studies.

Correspondence : Rani Balasubramanian, Deputy Director, Tuberculosis Research Centre, Indian Council of Medical Research, Chetput, Chennai- 600 031
Email : trcicmr@giasmd01.vsnl.net.in

These studies involved coordination with different collaborators, on day-to-day management of the patients admitted. The design of the study also had provision for change of treatment, in case of clinical deterioration or severe adverse reactions. Quite often, the diagnostic procedures were carried out in the feeding hospitals but all the clinical specimens were processed at the TB Research Centre.

In order to monitor these patients, liver and renal function tests, complete haemogram and complete examination of urine were carried out prior to treatment and also at periodic intervals during treatment and follow-up.

Diagnosis

The clinical manifestations varied depending on the anatomical site of involvement. Attempts were made to get tissue from the site of lesion for bacteriological and/or histo-pathological confirmation. Previously, bacteriological confirmation was reported only in 30 to 50% of patients, as these were pauci-bacillary conditions[4]. Hence all the biopsy specimens were cultured in multiple solid and liquid media namely, Lowenstein-Jenson's medium with or without pyruvate, Middlebrook's 7H11 medium and Kirschner's medium[14].

For evidence of TB elsewhere, chest radiographs, bacteriological examination of sputum, urine and biopsy specimens for *M. tuberculosis* were undertaken. Histo-pathological examination of biopsy specimens was also carried out.

Treatment Regimens

Short course chemotherapy (SCC) regimens for 6 to 12 months in various NPFTB are listed in Table 3. For all patients, each dose was administered under the direct supervision of a staff member for the initial 2 months. The patients attended the clinic as outpatients and were hospitalised only if they were sick.

RESULTS

Study Population and Follow-up

A total of 260 patients with TB spine, 180 children of age 12 years or below with TB meningitis, 239 children with TB lymphadenitis, 33 patients with Pott's paraplegia, 193 adults with abdominal TB and 108 patients with brain tuberculoma were enrolled for the studies. The period of follow-up ranged from 2 to 10 years.

Age and Sex Distribution

The non-pulmonary forms of TB occur in all age groups. The studies on TB lymphadenitis and TB meningitis were done exclusively on children aged 12 years and below. In TB meningitis study 84% of children were less than 4 yrs. and amongst them 31% were $\leq$ 1 yr old. About 46% with TB lymphadenitis were 54 yrs old. In our series, one third of TB spine population, 15% of patients with Pott's paraplegia, and 45% of brain tuberculoma patients were children. The study on abdominal TB included only adults.

While pulmonary tuberculosis is more common in adult males, most studies in peripheral lymph node tuberculosis have described a female preponderance. The proportion of females was 49% in TB lymphadenitis, 61% in brain tuberculoma, 56% in abdominal TB and 53% in TB meningitis.

Co-existence of TB in Other Organs

In our studies, evidence of pulmonary TB on X-ray was variable in different forms, ranging from 9 to 55% (Table 1).

Urine cultures were positive for *M. tuberculosis* in 14 of 259 patients with spinal TB and in 19 of 193 patients with abdominal TB, amongst whom 17 patients also had positive sputum cultures. One third of abdominal TB patients had evidence of other forms of TB.

Mantoux Test in Non-Pulmonary Form Tuberculosis

The Mantoux induration was >10 mm in 92% of TB spine,

TABLE 1: Mantoux Results and Radiographic Evidence of Pulmonary TB in TRC Studies

Studies	No. of patients	Positive Mx * %	X-ray evidence of P. TB %
TB spine	304	93	13
TB meningitis	180	50	55
TB lymphadenitis	197	81	24
Pott's paraplegia	33	63	48
TB abdomen	193	74	48
Brain tuberculoma	108	44	9

* Induration 10mm or more to Mantoux test

63% of Pott's paraplegia, 50% of TB meningitis, 44% of brain tuberculoma, 81% of TB lymphadenitis and 74% of abdominal TB.

Laboratory Confirmation of Diagnosis

The direct bacteriological and histo-pathological proofs of TB are listed in Table 2. In TB spine study, biopsy material was obtained from 85 patients, of whom culture for M. tuberculosis was positive in 50% of patients while 79% had histo-pathological proof of TB. Among 180 patients with TB meningitis, CSF culture for M. tuberculosis was positive in 33%. Both smear and culture examinations were done in 103 patients, and either smear or culture was positive for *M. tuberculosis* in 58%. Among 168 patients with TB lymphadenitis, 98% had histo-pathological and 62% had bacteriological proof of TB. Of 33 patients with Pott's paraplegia, specimens were available from 23 patients; of these 54% had bacteriological and 68% had histo-pathological confirmation. Among 193 patients with abdominal TB, 40% had bacteriological evidence and 51% had histo-pathological proof.

TABLE 2 : Laboratory Confirmation of Diagnosis in NPFTB

Studies	No. of patients	No. of specimens*	Bacteriological proof %	Histo-pathological proof %
TB spine	304	85	50	29
TB meningitis	180	180	33	
TB lymphadenitis	168	168	62	98
Pott's paraplegia	33	23	54	68
Abdominal TB	193	156	40	51
Brain tuberculoma	108	13		61

* includes biopsies, pus, sputum, CSF, urine and ascitic fluid.

Efficacy of Short Chemotherapy Course Regimens (Table 3)

The efficacy varied from 89 to 99% in all studies except in TB meningitis study where only about a third of the patients showed favourable response or improved.

Adverse Reactions to Drugs

Hepatitis was one of the major adverse reactions necessitating interruption or termination of drugs. Hepatotoxic drugs like rifampicin and isoniazid were withheld and substituted with streptomycin and ethambutol. However, these drugs were resumed after recovery from jaundice, uneventfully, in majority of patients.

Thirty nine percent of TB meningitis patients developed jaundice with isoniazid in the dose of 20 mg/kg (Table 4). In the subsequent studies when the dosage of isoniazid was reduced from 20 mg to 12 mg, only 16% developed hepatitis. There were more of hepatitis cases (21%) when pyrazinamide was added as the fourth drug to the regimen. However, hepatitis reduced drastically to 5% subsequently after rifampicin was given twice a week rather than daily. Hepatitis was slightly higher in patients exposed to surgery and to anaesthetic agents. Among TB spine cases the surgical series patients had 18% hepatitis, in comparison to 10% in the ambulatory series. A total of 12% of Pott's paraplegia patients, treated with surgery and chemotherapy, developed hepatitis and rifampicin was terminated in all. Among the paediatric TB lymphadenitis patients hepatitis was not a problem as only 1% developed jaundice.

Among abdominal TB patients, although overt involvement of liver was a clear possibility, only 17% developed hepatitis and rifampicin was terminated in 2 patients. The other serious toxicity was peripheral neuritis in 3% patients in whom isoniazid was terminated while ethambutol was terminated in 2% of patients who developed visual problems.

DISCUSSION

In India 10 to 15% of all forms of TB are reported to be NPFTB. Recently higher prevalence rates have been reported in the West; France had 25% and Canada 50%[15,16]. This problem is reported to be increasing in Western countries and Sub Saharan African regions partly due to dual infection of TB with HIV[17,18]. Since 1987, NPFTB has been accepted as an AIDS defining disease'. Shafer and coworkers in a retrospective study in New York found NPFTB to be as high as 43% among 464 AIDS patients[19].

One of the major pitfalls in the diagnosis of NPFTB is the clinical presentation of NPFTB which may be atypical and TB may not be considered at all in the differential diagnosis. In developing countries, the

TABLE 3 : Study Population and Efficacy of the Treatment Regimens

Studies	Rx. regimen	Duration (months)	No. of patients	Follow-up period (months)	Overall favourable response %
TB spine**	$6HR_7$+ Modified Hongkong Surgery	6	78	120	90
	$6HR_7$	6	78	120	94
	$9HR_7$	9	79	120	99
TB meningitis*	$2HRS_7/4HE_7S_2$ /$6HE_7$	12	69	24	33
	$2HRZS_7/10HE_7$	12	24	24	29
	$2R_2HZS_7/10HE_7$	12	70	24	36
Pott's paraplegia**	Radical surgery+ $2SHER_7/7HR_2$	9	20	60	90
	$2SHER_7/7HR_2$	9	11	60	73
TB lymphadenitis*	$2SHRZ_3/4SH_2$	6	168	36	97
Abdominal TB***	$2HRZ_7/4HR_7$	6	85	60	94
	$1EHS/10HE_7$ (1SEH/11EH)	12	93	60	87
Brain tuberculoma**	$3HRZ_7/6HR_2$	9	47	24	89
	$3HRZ_3/6HR_2$	9	44	24	91

H - Isoniazid; R - Rifampicin; Z - Pyrazinamide; E - Ethambutol S - Streptomycin
* Only paediatric patients ; ** Both paediatric and adult patients; *** Only adult patients

problem of diagnosis is compounded by lack of diagnostic resources with few forms of extra-pulmonary TB being positive bacteriologically. Empirical treatment or trials of treatment are being prescribed only on clinical grounds without pathological and/or bacteriological support or confirmation. Diagnosis made only on clinical grounds leads to over-diagnosis and unnecessary treatment of a large number of patients[20]. This was clearly brought out in our study where, out of 373 biopsies done after the clinical diagnosis of TB lymphadenitis, only 126 (34%) showed histo-pathological confirmation to support the diagnosis[21].

A high index of suspicion in developing countries is necessary to make an early diagnosis, especially in TB abdomen, which simulates a number of inflammatory and neoplastic conditions. In order to help in early diagnosis a clinical algorithm has been developed based on the findings of our study. Pain in the right iliac fossa coupled with tenderness of abdomen or alteration of bowel habits or increased borbrygmi or distension of abdomen of more than one month should make one suspect abdominal TB[13].

In clinical practice the cutaneous reaction to PPD is usually used as a diagnostic aid for TB. Its value is limited in adults in India, since about 40% of the adult population is infected with TB[22]. However, it may be of use in children aged 5 years or below as shown in our TB lymph study, where 50% of children had very large reactions (30mm or more) often with ulceration. These large reactions were quite unique to TB lymphadenitis as it was not observed in other forms of NPFTB[21].

Attempts should always be made to confirm the diagnosis by histo-pathological or bacteriological examinations in NPFTB. In our studies, wherever relevant, the diagnosis was confirmed by undertaking smear and culture examination of specimens, including biopsy, sputum, urine and ascitic fluid in multiple liquid and solid media[14]. The culture positivity varied from 33 to 62%. These proportions are comparable to those reported earlier[4,5]. Use of multiple culture media is recommended since NPFTB is essentially a paucibacillary condition and to get a bacteriological confirmation, no effort should be spared. Atypical mycobacteria implicated in NPFTB disease were not observed in our series.

Selection of the diagnostic procedures depends on the organ involvement in NPFTB. Laparoscopy with target peritoneal biopsy is the current investigation of choice in the diagnosis of peritoneal tuberculosis. Direct inspection alone will allow an accurate presumptive diagnosis in 80 to 95% of patients as the appearances of yellowish white miliary tubercles over the peritoneum and the erythematous patches and adhesions are very characteristic. In addition the biopsy specimens may demonstrate acid-fast bacilli or caseating granulomas in more than 75% of patient?. Fine needle aspiration of lymph nodes and cytological examination plus AFB smear and culture examination appear to be the diagnostic

TABLE 4 : Adverse Reactions

Studies	Regimen	Dosage of drugs (mg/kg) R	H	Z	Hepatitis %
TB spine	Hongkong Surgery + $6HR_7$	10 to 12	6 to 10		18*
	Amb $6HR_7$ + $9HR_7$	10 to 12	6 to 10		10
TB meningitis	$2HRS_7/4HE_7S_2/6HE_7$	12	20		39
	$2HRS_7$ / $4EH_7S_2/6HE_7$	12	12		16
	$HRZS_7$ / $10HE_7$	12	12	35	21
	R_2HZS_7 / $10HE_7$	12	12		5
TB lymphadenitis	$2HRZS_3/4HS_2$	10	15		1
Pott's paraplegia	$2HRES_7/7HR_2$ + Surgery	10-12	6 - 10		12**
Abdominal TB	$2HRZ_7/4HR_7$	10	5-8		17
	HES_7 / $11EH_7$		5-8	25	4
Brain tuberculoma	$3HRZ_7$ / $6HR_2$	12	10		12
	$3HRZ_3$ / $6HR_2$	12	15		0

* Rifampicin terminated in one patient

** Rifampicin terminated in two patients

procedures of choice in superficial TB lymphadenitis[24]. However, if the FNAC exam results are inconclusive, excision biopsy may need to be done. In our study all lymphadenitis patients had open biopsy.

More than one procedure is often necessary for confirmation of the diagnosis. For example, undertaking different relevant diagnostic procedures such as liver biopsy, barium meal series, bacteriological and biochemical examination of ascitic fluid in different types of abdominal TB patients enabled us to establish the diagnosis in 72% of patients. In our series of 60 cases suspected of peritoneal TB, the diagnosis was confirmed by laparoscopy in 82%[13]. Thus the proportion of patients with a diagnostic confirmation was much higher in our series compared to earlier[25] reports.

Even though a number of reports on molecular biological tests like SAFA, ELISA, slide agglutination techniques and PCR are available in NPFTB, the specificity and sensitivity of these tests are variable[26].The results need to be interpreted in the light of clinical findings. Smith et al advocated the use of PCR in clinical specimens as the results were comparable to that of M. *tuberculosis* culture[27]. From our centre, it was reported that adenosine deaminase level of 4U/L and above and lysozyme activity level of 2 mg/L or more could provide additional supportive evidence for the diagnosis of TB meningitis in clinically suspected and bacteriologically negative cases[28]. It was also reported that use of ADA in ascitic fluid was a sensitive and specific marker approaching 100% in the diagnosis of peritoneal TB[28a] It was recently reported that demonstration of mycobacterial antigens in tissue specimens discriminates between an active and a resolving granuloma. In the absence of intact bacilli, antigenic fragments of *M. tuberculosis* could be detected in the tissue. This may be more sensitive than finding the bacilli[29].

Several RCTs over the last two decades have established the role of SCC as the main treatment for sputum positive TB and have stimulated research into shorter regimens for the treatment of NPFTB[30]. All our studies at TRC on TB spine, TB lymphadenitis, Pott's paraplegia, abdominal TB and brain tuberculoma have clearly established the efficacy of SCC (6 to 9 months) in both children and adults[7-13]. The overall favourable response varied from 87 to 99% except in Pott's paraplegia (73%). Intermittent regimens have been proven as effective as daily regimens. These patients have been followed up systematically for a minimum period of 5 years to a maximum period of 10 years. The relapse rates during long time follow-up period have been less than 4% in all studies. For the first time, fully intermittent chemotherapy

was shown to be effective in the treatment of brain tuberculoma[11].

The current recommendations for the management of NPFTB by international agencies are as follows: The International Union against TB and lung diseases and the Joint Tuberculosis Committee of the British Thoracic Society has recommended a 6-month regimen ($2HRZ_7$ / $4HR_7$) for all forms of NPFTB except severe forms (meningitis and bone and joint TB) where the duration is extended to 12 months[13]. The WHO has recommended a 9-month regimen ($2SHRZ_7/7RH_7$) for all NPFTB except severe forms (miliary and meningeal) where the duration is extended by 3 months[32].

Even though chemotherapy gives good results in most of the NPFTB, there are exceptions like meningitis and Pott's spine where the outcome depends on early diagnosis. In TB meningitis study the outcome in children treated with SCC for 12 months was related to the stage of the disease at the time of initiating treatment[9]. Others have reported similar findings; predictors of poor outcome were younger age and advanced stage and the neurological sequelae were directly related to the stage of the disease and the duration of symptoms prior to admission[33,34]. Changes in the treatment policies and the introduction of SCC did not influence the prognosis of TB meningitis. Similarly, in Pott's paraplegia series, the time taken for neurological recovery was not related to the type of management but appeared to be influenced by factors such as initial motor power, presence or absence of bed sores and duration of kyphosis[10]. These findings emphasise the importance of early diagnosis and treatment in TB meningitis and Pott's paraplegia. Thus prevention is more important especially in severe forms of TB. Case control studies show that BCG is effective in prevention of NPFTB[35,36].

The British Medical Research Council investigated the relative role of surgery and chemotherapy in the management of TB spine patients in many RCTs[37]. It was concluded that operative procedures were unnecessary and ambulatory SCC regimens were highly effective. Similarly, our study on TB spine has shown that SCC of 6 months duration is adequate in adults and surgery is indicated only in patients aged less than 15 years and having an initial angle of kyphosis more than $30^{0.2}$ Similar observations were made by Upadhyay et al in children with spinal TB[38].

Similarly in Pott's paraplegia patients in our series, SCC of 9 months was proven to be adequate in 8 of 29 patients and surgery was resorted to only if there was no improvement in clinical condition or if the condition worsened, despite SCC for 2 months[10].

Conclusion

- Increase in NPFTB incidence globally due to HIV epidemic
- Diagnosis demands a high index of suspicion
- Diagnosis based on clinical findings alone leads to over treatment
- All attempts should be made to get bacteriological and/or histo-pathological confirmation.
- Delay in diagnosis leads to sequelae in severe forms of TB
- More than one diagnostic procedure is often needed for confirmation of the diagnosis.
- TRC studies have proven the efficacy of SCC in most forms of NPFTB. SCC regimens containing 3 or 4 bactericidal drugs for 2 or 3 months followed by 2 drugs for 4 to 6 months is adequate. Intermittent SCC regimens are as effective as daily chemotherapy.
- No role for routine surgery except in a few special situations.

REFERENCES

1. Pitchenik AE, Cole C et al. Tuberculosis, atypical mycobacteriosis and AIDS among Haitian and non Haitian patients in South Africa. *Ann Intern Med* 1984; 101: 641-645.
2. Harries AD. TB and HIV infection in developing countries. *Lancet* 1990; 335: 387-390.
3. Medical Research Council. TB and Chest Diseases Unit. National Survey of notifications of tuberculosis in England and Wales in 1988. *Thorax* 1992; 47: 770-775.
4. Dutt AK and Stead WW. Short course chemotherapy for extra pulmonary TB. *Annals Intern Med* 1986; 104: 7-12.
5. Salvador Alverz, William Meccabe R. Extrapulmonary TB. Revisited: *Review of Experience at Boston City and Other Hospitals.* Williams & Wilkines & Co. 1984; 25-55.
6. Ormerod LP. *The Management of Extrapulmonary Tuberculosis in Mycobacteria.* Gangadaram PRJ (ed). International Thomson Publishing Co. 1997; pp. 236-278.
7. Indian Council of Medical Research/British Medical Research Council. A controlled trial of short course regimens of chemotherapy in patients receiving ambulatory treatment or undergoing radical surgery for tuberculosis of the spine. *Indian J Tub* 1989; 36(suppl.): 1-21.
8. Tuberculosis Research Centre. Short course chemotherapy for tuberculosis of the spine. A comparison between ambulatory treatment and radical surgery 10 year report *J Bone Joint Surg (Br).* 1998; 81: 464-471.
9. Ramachandran P, Duraipandian M, Nagarajan M, Prabhakar R, Ramakrishnan CV, Tripathy SP. Three chemotherapy studies of tuberculous meningitis in children. *Tubercle* 1986; 67: 17-29.
10. Rajeswari R, Balasubramanian R, Venkatesan P. Short-course

chemotherapy in the treatment of Pott's paraplegia: report on five year follow. *Int J Tuberc Lung Dis 1997;* 1(2): *152-158.*

11. Rajeswari R, Sivasubramanian S, Balambal R. A controlled clinical trial of short-course chemotherapy for tuberculoma of the brain. *Tubercle Lung Dis.* 1995; 76: 111-117.
12. Jawahar MS, Sivasubramanian S, Vijayan V. Short course chemotherapy for tuberculous lymphadenitis children. *Br Med J* 1990; 301: 359-362.
13. Balasubramanian R, Nagarajan M, Balambal R. Randomised controlled clinical trial of short course chemotherapy in abdominal tuberculosis: a five-year report. *Int J Tuberc Lung Dis* 1997; 1(1): 44-51.
14. Paramasivan CN, Vanaja Kumar, Alexander C *et al.* Use of multiple media for the cultivation of mycobacteria from specimens other than sputum. *Indian J Med Res* 1987; 86: 290-294.
15. Stealianides S, Belmatoug N, Fantin B. Manifestation and diagnosis of extrapulmonary tuberculosis. *Rev Mal Respir* 1997; 14: 872-887.
16. Cowie RL, Sharpe JW. Extra-pulmonary TB: a high frequency in the absence of HIV infection. *Int J Tuberc Lung Dis* 1997; 1(2): 159-62.
17. Sudra P, Hirshchel BJ, Gatell JM *et al.* TB among European patients with AIDS. *Tuberc Lung Dis* 1996; 77(4): 322-8.
18. Watters DA. Surgery for TB before and after HIV: a tropical perspective. *Br J Surg* 1997; 84(1): 8-14.
19. Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency infection. *Medicine* 1991; 70: 384-97.
20. Ramanathan M, Wahi Nuddin S, Safain E, Sellaia SP. Abdominal TB, a presumptive diagnosis. *Singapore Med J* 1997; 38(9): 364-68.
21. Jawahar MS. Tuberculosis of superficial lymph nodes. *Karnataka Medical Journal.* Vol. 68 (No. 2): 23-29.
22. Central TB Division. Directorate General of Health Services, New Delhi, India. *Technical Guidelinesfor TB Control* 1998.
23. Bhargava BK, Shrinivas MD, Chopra P et al. Peritoneal TB: laparoscopic patterns and its diagnostic accuracy. *Am J Gastroenterol* 1992; 87: 109-112.
24. Prasad RR, Narsimhan, Sankaran V, Neliath AJ. Fine needle aspiration cytology in the diagnosis of superficial lymphadenopathy: an analysis of 108 cases. *Diagnosis Cytopathol* 1996; 15(5): 382-386.
25. Chang HT, Leu S. Hsu, Lui WY. Abdominal tuberculosis-a retrospective study of 121 cases. *Chung Hua 1 Hsuch Tsa Chih* 1991; 47(1): 24-30.
26. Rapid Diagnostic Tests for Tuberculosis. Progress but no Gold Standard. Editorial. *Am J Respir Crit Cure Med 1997;* 155: 1497-1498.
27. Smith KC, Starke JR, Fishena CH, Onglt K, Derby M. Detection of *M. tuberculosis* in clinical specimens from children using PCR. *Paediatrics* 1996; 97(2): 155-160.
28. Selvakumar N, Vanajakumar, Duraipandian M, Thilothammal N and Prabhakar R. Cerebrospinal fluid adenosine deaminase and lysozyme levels in the diagnosis of TB meningitis. *Indian J Tub* 1991; 38: 217-220.

28a. Martin RE, Bradsher RW. Elusive diagnosis of TB peritonitis. *South Med J* 1986; 79: 1076-1079.

29. Shakila H, Jayashankar K and Ramanathan VD. The clearance of tubercle bacilli & mycobacterial antigen vis-a-vis the granuloma in different organs of guinea pigs. *Indian J Med Res* 1999; 110: 4-10.
30. Girling DJ, Derbyshire JH, Humphries MJ et al. Extrapulmonary TB *Br Med Bull* 1988; 44: 738-756.
31. Chemotherapy and management of tuberculosis in the United Kingdom. Recommendations of Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 1990; 45: 403-408.
32. Framework for effective tuberculosis control. WHO Global Tuberculosis Programme 1994, WHO/TB/94. 179.
33. Girgis N, Sultan Y, Farid Z et al. TB Meningitis. Abbasia Fever Hospital Cairo, Egypt from 1976-1996 *Am J Trop Med Hyg* 1998; 58 (1): 28-34.
34. Humphries MJ, Teoh R, Lure J and Gabriel M. Factors of prognostic significance in Chinese children with tuberculous meningitis. *Tubercle* 1990; 71: 161-168.
35. Zodpey SP, Maldhure BR, Dehankar AG, Shrikhande SN. Effectiveness of BCG vaccination in non-pulmonary forms of TB. A case control study. *J Commun Dis* 1396; 28(2): 77-84.
36. Fishov W, Decashsho EA, Radiogues LC, Hattly SRA. Effectiveness of BCG vaccination against TB meningitis : a case control study in Sao Paulo Brazil. *Bull WHO* 1990; 68: 69-74.
37. Thirteenth report of MRC working party on TB of spine. A 15 year assessment of controlled trials of the management of TB of the spine in Korea and Hongkong. *J Bone Joint Surg Br* 1998; 80(3): 456-462.
38. Upadhyay SS, Saji MS, Sell P, Hsu LC, Uay AC. The effect of age on the change in the deformity after anterior debridement surgery for TB spine. *J Bone Joint Surg* 1994; 76-A: 701-8.