

ORIGINAL ARTICLE

A real-world experience with 6 months of antitubercular therapy in abdominal tuberculosis

Harshal S Mandavdhare,  Harjeet Singh,  Usha Dutta and Vishal Sharma 

Department of Gastroenterology and General Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Key words

hepatitis, intestinal tuberculosis, peritoneal tuberculosis, surgery.

Accepted for publication 4 December 2018.

Correspondence

Vishal Sharma, Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India.
Email: docvishalsharma@gmail.com

Declaration of conflict of interest: None.

Abstract

Background and Aim: Abdominal tuberculosis is an important form of extrapulmonary tuberculosis. Evidence from clinical trials suggests that 6 months of antitubercular therapy (ATT) is sufficient for abdominal tuberculosis.

Methods: We report real-world experience with 6 months of ATT based on a retrospective analysis of patients with abdominal tuberculosis seen at a large tertiary care hospital in India.

Results: Of 101 patients, 93 with complete records were included. The mean age was 35.90 ± 14.06 years, and 53 were males (56.98%). A total of 42 patients (45.16%) had intestinal involvement, 24 (25.08%) had peritoneal, 22 (23.65%) had combined involvement, and 5 patients (5.37%) had isolated lymph nodal involvement. Six patients received prolonged ATT. Six patients developed ATT-induced hepatitis. Of 64 patients with intestinal involvement, 45 had stricturing disease (70.3%), of whom 7 (15.5%) required surgery due to refractory symptoms. Overall, there was one death, and eight patients (including one with massive gastrointestinal bleeding) needed surgery.

Conclusion: Six months of ATT is associated with objective clinical response in most of the patients of abdominal tuberculosis.

Introduction

Tuberculosis is an important cause of morbidity and mortality in the developing world. The diagnosis and treatment of extrapulmonary tuberculosis is challenging. The appropriate duration of therapy for many forms of extrapulmonary tuberculosis is uncertain, and longer treatment regimens are recommended for spinal and neurological forms of tuberculosis.¹ This is due to concerns regarding the penetrability of antitubercular drugs in these tissues and a belief that longer regimens may prevent relapses.

Abdominal tuberculosis is an important form of extrapulmonary involvement, which is especially challenging to diagnose because of difficulty in the acquisition of tissues and also because it closely mimics certain conditions like Crohn's disease and malignancy.^{2,3} Furthermore, the sequelae of intestinal tuberculosis, like pain resulting from intestinal strictures or peritoneal adhesions, may be confused with ongoing disease activity, persuading clinicians to prescribe a longer duration of treatment. A recent multicenter randomized trial from India utilized directly observed treatment strategy, and the drugs were administered on alternate days (intermittent therapy), which suggested equal efficacy with either 6 or 9 months of treatment.⁴ In addition, a Cochrane systematic review of three eligible reports suggested that the use of 6 months of treatment seemed to be adequate.⁵ These trials prompted a change in treatment strategy, with 6 months of treatment being used in most. Recent Indian

guidelines recommend 6 months of antitubercular therapy for abdominal tuberculosis (peritoneal and intestinal).¹ However, the excellent results obtained in a clinical trial setting where the patient selection, interventions, and follow-up are streamlined may not be replicated in real-life settings. Important measures of outcome in patients with abdominal tuberculosis would include subjective parameters (pain resolution, defervescence of fever, weight gain, and gain of appetite) and objective parameters (ulcer healing and ascites resolution).^{6–8}

Therefore, we conducted a retrospective study of treatment outcomes in a real-life setting where, predominantly, a 6-month daily treatment strategy was used in the treatment of patients. We report the clinical profile and outcomes with this treatment strategy in our cohort of patients.

Methods

We conducted a retrospective analysis of our prospectively collected database of patients who were diagnosed and treated for abdominal tuberculosis with antitubercular therapy. The study was conducted at a large tertiary care center in North India over a period of 1.5 years. The study was cleared by the institute's ethical committee, and the need for informed consent was waived. However, patients gave consent prior to any procedure like colonoscopy or fine-needle aspiration or ascitic tap.

Diagnosis and case definition. The diagnosis of abdominal tuberculosis was based on a combination of clinical, radiological (on computed tomography scan bowel thickening (Fig. 1), ascites, peritoneal and/or omental thickening, necrotic lymph nodes, matting of bowel loops with formation of cocoon), biochemical [high adenosine deaminase (ADA) > 32 U/L and low serum ascitic albumin gradient in the ascitic fluid], microbiological [positive acid fast bacilli (AFB) in fluid or tissue], and histological (presence of granulomas with or without caseation necrosis).

A case was defined as a confirmed case of abdominal tuberculosis if it fulfilled one of the following criteria⁷:

1. Microbiological evidence of the presence of AFB in tissue or fluid or positive culture of the same specimen
2. Presence of caseation necrosis in the tissue specimen

A case was considered a clinically diagnosed case when, apart from clinical and radiological evidence of abdominal tuberculosis, one of the following features was present:

1. Histology showing granulomas and/or chronic inflammatory infiltrate
2. Peritoneal fluid shows high ADA values (>32 U/L)
3. Exclusion of other differential diagnosis by tissue biopsy and/or cytological analysis of fluid and demonstration of objective response to therapy in the form of mucosal (ulcer) healing or ascites reduction/resolution⁷⁻⁹

The diagnosis of stricturing disease was made on the basis of either endoscopic evidence of stricture or radiological evidence of narrowing with proximal dilatation.

Evaluation and follow-up. The clinical details, including the presentation, associated comorbidities, details of imaging and colonoscopic findings like ulcers (Fig. 2) and strictures, and hematological and biochemical investigations, were recorded in proforma. The data on clinical outcomes, pain while on treatment, and need for surgery were also recorded. We started standard weight-based antitubercular therapy (ATT) with four drugs (rifampin, isoniazid, pyrazinamide, and ethambutol) for the patients, which was given on a daily basis except to those who received directly observed treatment short course (DOTS). Presently, in India, there is a change in treatment programs, and daily

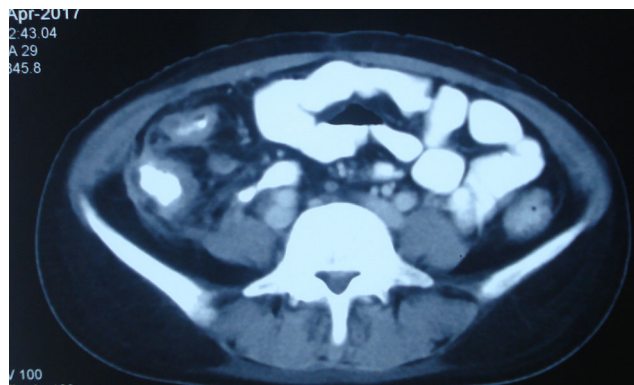


Figure 1 Computed tomography showing thickened ascending colon and caecum.

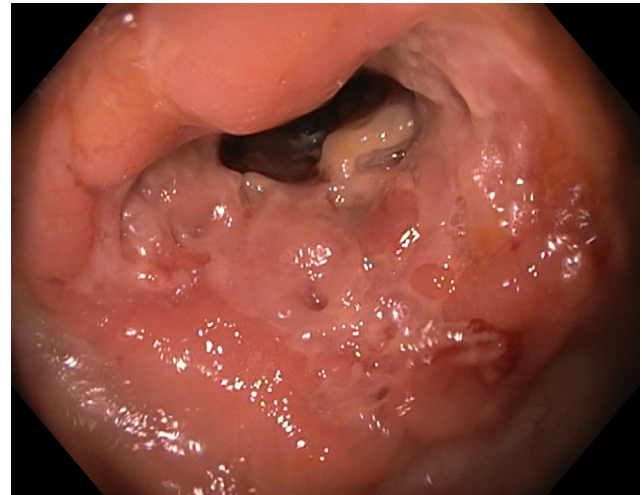


Figure 2 Colonoscopic image showing circumferential ulceration with narrowing.

DOTS is being given in a phased manner at different centers. The patients were followed up every 2 weeks for the first month and then every month till outcome in the form of successful completion of 6 months' ATT or prolongation of ATT and further outcome as improvement or need for surgery. ATT was prolonged in cases where adequate response was deemed not to have been achieved. Patients with modified ATT (for underlying liver disease or ATT hepatitis) also received longer regimens. During follow-up, we performed clinical assessment for response and did periodic liver function tests (monthly or if symptomatic) to keep a check on ATT-induced hepatitis and carried out the necessary drug modification or stoppage and reintroduction as per the case. The response to the ATT was also assessed using clinical and objective parameters. The patients underwent assessment of weight gain, improvement of appetite, and historical assessment of symptomatic response. In addition, at 2 months, mucosal healing with colonoscopy for intestinal tuberculosis and resolution of ascites using ultrasonography for peritoneal tuberculosis was sought. In cases where the response was not achieved, we considered the possibilities of alternative diagnosis and drug-resistant tuberculosis. For lymph-nodal tuberculosis, response was assessed using abdominal ultrasonography. The present study only reports on those patients who achieved a clinical and objective response, thereby confirming the diagnosis of tuberculosis at the outset, and completed at least 6 months of follow-up. The patients with alternative diagnosis (seven had Crohn's disease) were excluded. The patients with underlying cirrhosis received modified ATT depending on the severity of liver disease as assessed by Child Pugh class.

We report the clinical outcomes, need for ATT modification, need for surgery, and mortality in our cohort of patients with abdominal tuberculosis.

Results

Clinical profile. Of the 101 patients seen over the study period, complete follow-up was available for 93 patients. We

included these 93 patients for analysis, and these formed part of the study (Figs 3 and 4). The mean age of the study subjects was 35.90 ± 14.06 years (range 13–80 years). The duration of symptoms varied from 10 days to 4 years, with a median duration of 7 months. Of the 93 patients, 53 were males (56.98%). The clinical presentation in decreasing order was abdominal pain in 89 of 93 (95.7%), loss of weight and appetite in 73 of 93 each (78.5%), fever in 63 of 93 (67.74%), episode of intestinal obstruction in 30 of 93 (32.25%), lump abdomen in 10 of 93 (10.75), bleeding per rectum in 6 of 93 (6.4%), and diarrhea in 4 of 93 (4.3%). Of the study subjects, 20 had various associated comorbidities, which included diabetes mellitus in 4 (of whom 1 each also had chronic hepatitis B, benign prostatic hyperplasia); chronic liver disease in 4 (2 due to alcohol and 1 each due to hepatitis C related and cryptogenic); hypothyroidism in 3; hypertension in 2 (1 also with Parkinson’s disease); gallstones disease in 2; seizure disorder in 2; and 1 each had chronic pancreatitis, chronic kidney disease, carcinoma cervix, chronic obstructive airway disease, extrahepatic portal vein obstruction, nephrotic syndrome, and postpolio scoliosis. Two patients were human immunodeficiency (HIV) positive. Of the 68 patients who had Mantoux test results available, 49 had positive results (72.05%). Thirty-five patients had ascites (37.63%), of whom 30 had high ADA (>32 U/L) values (85.71%). Of the 32 patients who had serum ascites albumin gradient (SAAG) values available, 30 had low SAAG values (93.75%), and the 2 patients with high SAAG (>1.1 g/dL) had underlying cirrhosis. Based on combined radiological and endoscopic findings, we categorized the patients per involvement of intestine, peritoneum, and lymph nodes alone or in combination. Isolated intestinal and peritoneal involvement was seen in 16 (17.202%) and 14 (15.05%) patients, respectively; combined intestinal and peritoneal involvement in 9 (9.67%); isolated lymph-nodal involvement in 5 (5.37%); combined intestinal and lymph nodal in 26 (27.9%); combined peritoneal and lymph-nodal involvement

in 10 each (10.75%); and involvement of all three (intestinal + peritoneal + lymph nodal) in 13 (13.97%) patients. Interestingly, of the 20 patients (21.5%) who were confirmed cases of abdominal tuberculosis (positive AFB in tissue and or caseation), 8 had combined intestinal and lymph nodal involvement, 3 had isolated intestinal involvement, 5 had combined intestinal and peritoneal involvement, 2 had isolated lymph nodal involvement, and 2 had combined peritoneal and lymph nodal and isolated peritoneal involvement, respectively (Fig. 3). Of the patients with intestinal involvement, the most common locations were terminal ileum (27 patients), caecum (23), ileocecal junction (16), and other areas of the colon (16). Finally, when patients were evaluated for extra-abdominal involvement, we found 27 of 93 (29.03%) with associated extra-abdominal tuberculosis, of whom 15 (55.6%) had pulmonary parenchymal involvement; 7 (25.92%) had pleural involvement; 2 had combined pulmonary and pleural involvement; and 1 each had genitourinary tuberculosis, pulmonary and central nervous system involvement, and mesenteric and pleural involvement.

Antitubercular therapy and outcomes. Of the 93 patients, 90 patients were initiated on standard ATT, which included four drugs for the initial 2 months, followed by two drugs for the next 6 months. Initially, three patients with underlying cirrhosis were started on modified therapy. One of the patients with cirrhosis died during the treatment. Six patients received prolonged antitubercular therapy (9 months or more), whereas 87 patients received 6 months of treatment. Of the six patients, the reasons for prolongation were underlying chronic liver disease in two patients and thereby receiving modified ATT, persistent collections in two, and defaulter to treatment and disseminated disease [with central nervous system (CNS) involvement] in 1 each. Of the four patients with cirrhosis, one died at 2 months of complications related to cirrhosis. This patient had Child C cirrhosis and received no hepatotoxic drug. Of the remaining three patients with cirrhosis, one patient had Child A cirrhosis and received usual ATT, while in two patients with Child B cirrhosis, we replaced two hepatotoxic drugs (rifampicin and pyrazinamide with levofloxacin and streptomycin).

Overall, six patients (6.45%) started on standard ATT developed ATT-induced hepatitis, of whom we were able to successfully reintroduce ATT in five patients, except one patient for whom pyrazinamide was not reintroduced. The drugs were reintroduced on a weight-based dosage in order of rifampicin, isoniazid, and pyrazinamide. One patient developed a severe drug reaction to rifampicin, with fever, rigors, uneasiness, and rash, and was not given rifampicin again. For this patient, we replaced rifampicin with levofloxacin.

Of the 64 patients with intestinal involvement, 45 patients had stricturing disease at presentation (70.3%), of whom 22 patients (48.9%) experienced episodes of pain while they were on treatment; however, only 7 patients (15.6%) required surgery due to refractory stricturing disease (Fig. 4). At end of therapy, some abdominal pain was still present in 15 patients. Five of these cases underwent endoscopic dilatation for treatment of colonic strictures after the end of therapy, with symptomatic response. One patient needed surgery for massive gastrointestinal bleeding. Overall, 56 patients with intestinal involvement improved without surgery. Therefore, overall, eight patients (8.6%) needed surgery, while there was one mortality.

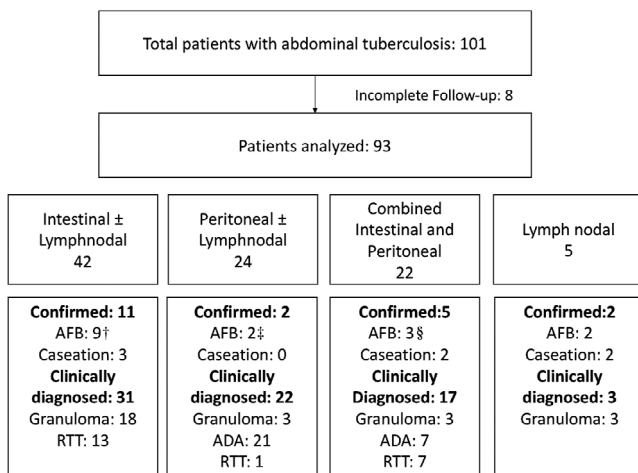


Figure 3 Chart showing patterns of involvement in patients with abdominal tuberculosis. †AFB positivity from sputum in five and intestinal tissue in four. ‡One pulmonary and one from peritoneal FNA. §All pulmonary. ADA, adenosine deaminase; AFB, acid fast bacilli; RTT, response to therapy.

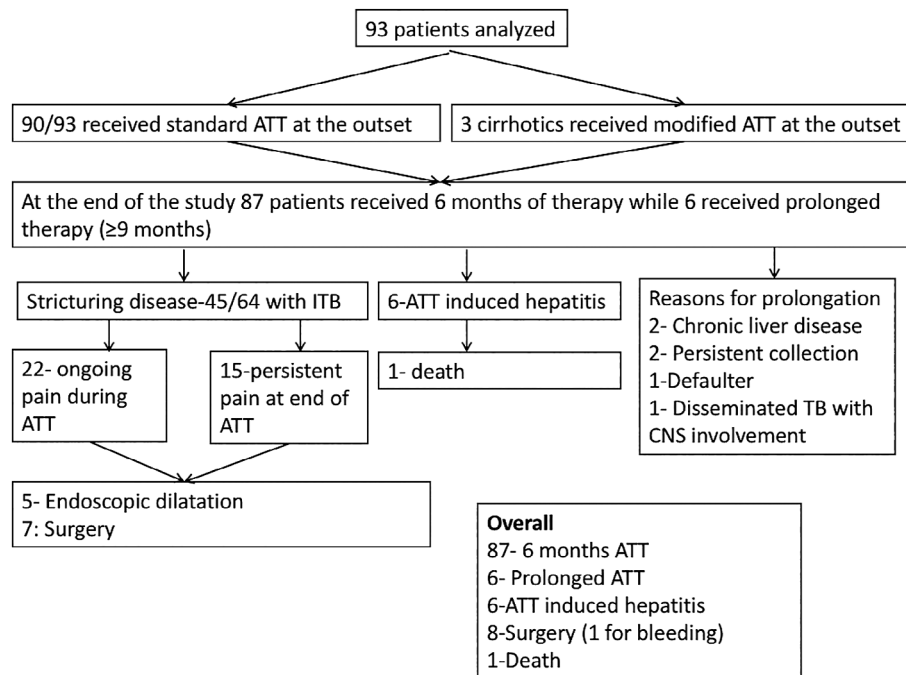


Figure 4 Outcomes in patients with abdominal tuberculosis. ATT, antitubercular therapy; CNS, central nervous system; ITB, intestinal tuberculosis; TB, tuberculosis.

Discussion

Abdominal tuberculosis is a complex entity that includes involvement of the gastrointestinal tract (small and large intestine), peritoneum, abdominal lymph nodes, and visceral organs (e.g. spleen, liver, pancreas etc).⁶ Although peritoneal tuberculosis is considered the most common form of abdominal tuberculosis, the higher fraction of our patients had intestinal involvement.² This may be related to the fact that intestinal tuberculosis is more difficult to diagnose and is more likely to present to a tertiary center, while facilities for abdominal paracentesis may be available at secondary care institutions, limiting the number of patients referred to or seen at the tertiary institutions. The diagnosis of abdominal tuberculosis is difficult for multiple reasons: need for specialized tests like colonoscopy, image-guided needle aspiration for cytology and microbiology, and low rates of histological (caseating granulomas) or microbiological positivity.⁴ Often, the clinicians have to resort to therapeutic trials and adequate response to treatment is one of the criteria proposed for diagnosis of abdominal tuberculosis.⁷⁻⁹ Not surprisingly, only 21% of our patients had a confirmed diagnosis of tuberculosis at the time of initiation of treatment, while the rest had clinically diagnosed tuberculosis, which was confirmed by way of objective documentation of response (mucosal healing or resolution of ascites or reduction in lymphadenopathy). The management of abdominal tuberculosis is also complicated by the fact that the assessment of response is difficult. In our cohort, we have used repeated colonoscopy at 2–3 months of ATT for intestinal tuberculosis and abdominal ultrasonography for resolution of ascites to document clinical response. Even so, 22 of our patients continued to be symptomatic, suggesting that the

intestinal strictures and adhesions that may be the sequelae of abdominal tuberculosis continue to take a toll on the patients even after a healing of underlying lesions is achieved with antitubercular therapy. Furthermore, at end of therapy, 15 patients still had abdominal pain, and 5 need endoscopic dilatation. In our cohort, eight patients required surgical intervention, and the most common reason was related to the recurrence of symptoms of intestinal obstruction while on ATT. While one patient needed surgery early on for massive gastrointestinal bleeding, of the other seven patients, only one who had associated peritoneal tuberculosis required surgery for intestinal obstruction related to adhesions at 1 month of ATT. The rates of surgery in our cohort suggest that stricture resolution may not occur in all patients who therefore need surgery. The data regarding the response of strictures to ATT is contradictory. An earlier report suggested that stricture healing is common, and 91% of patients with intestinal stricture improved with ATT, and only 8% needed surgery.¹⁰ Furthermore, in one of trials of 6 months' treatment, the rates of surgery were low, and only 2 of the 197 patients randomized needed surgery, while 6 patients died.⁴ Other trials did not report details of surgical interventions. In contrast, a recent retrospective report of 286 patients with intestinal tuberculosis (TB) suggested that only 66% patients of the 106 patients with stricturing disease had symptomatic improvement.¹¹ Even in the present report, of 45 patients with stricturing disease, 15 continued to be symptomatic even after completion of antitubercular treatment, and 8 (17.8%) needed surgery. Based on our findings (of persistent pain) and the recent report suggesting that strictures could persist despite adequate ATT, we feel that additional therapeutic interventions (like use of steroids with ATT) may be considered in future trials to ensure stricture resolution apart from mucosal

healing in patients with intestinal tuberculosis having stricturing disease.¹¹ None of the patients in this study were administered any steroids.

While the present study is limited by the retrospective design and nonrandomized nature, the strengths are that the data had been collected prospectively and that the study presents the real-life issues in management, and none of the patients were excluded a priori. In the randomized trials comparing 6 and 9 months of therapy, many patients with comorbidities like chronic liver disease and HIV were excluded. To conclude, 6 months of ATT is associated with objective clinical response (mucosal healing and ascites resolution) in most of the patients, but some patients continue to be symptomatic with sequelae of abdominal tuberculosis, which may warrant additional intervention in the form of endoscopic dilatation or surgical resection.

References

- Sharma SK, Ryan H, Khaparde S *et al.* INDEX-TB guidelines: guidelines on management of extrapulmonary tuberculosis of India. *Indian J. Med. Res.* 2017; **145**: 448–63.
- Limsrivilai J, Shreiner AB, Pongpaibul A *et al.* Meta-analytic bayesian model for differentiating intestinal tuberculosis from Crohn's disease. *Am. J. Gastroenterol.* 2017; **112**: 415–27.
- Sharma V, Bhatia A, Malik S, Singh N, Rana SS. Visceral scalloping on abdominal computed tomography due to abdominal tuberculosis. *Ther. Adv. Infect. Dis.* 2017; **4**: 3–9.
- Makharia GK, Ghoshal UC, Ramakrishna BS *et al.* Intermittent directly observed therapy for abdominal tuberculosis: a multicenter randomized controlled trial comparing 6 months versus 9 months of therapy. *Clin. Infect. Dis.* 2015; **61**: 750–7.
- Jullien S, Jain S, Ryan H, Ahuja V. Six-month therapy for abdominal tuberculosis. *Cochrane Database Syst. Rev.* 2016; **11**: CD012163.
- Mandavdhare HS, Singh H, Sharma V. Recent advances in the diagnosis and management of abdominal tuberculosis. *EMJ Gastroenterol.* 2017; **6**: 52–60.
- Sharma V, Mandavdhare HS, Lamoria S, Sigh H, Kumar A. Serial C-reactive protein measurements in patients treated for suspected abdominal tuberculosis. *Dig. Liver Dis.* 2017; **50**: 559–62.
- Sharma V, Mandavdhare HS, Dutta U. Letter: mucosal response in discriminating intestinal tuberculosis from Crohn's disease—when to look for it? *Aliment. Pharmacol. Ther.* 2018 Mar; **47**: 859–60.
- Logan VS. Anorectal tuberculosis. *Proc. R. Soc. Med.* 1969; **62**: 1227–30.
- Anand BS, Nanda R, Sachdev GK. Response of tuberculous stricture to antituberculous treatment. *Gut.* 1988; **29**: 62–9.
- Aggarwal P, Kedia S, Sharma R *et al.* Tubercular intestinal strictures show a poor response to anti-tuberculous therapy. *Dig. Dis. Sci.* 2017; **62**: 2847–56.